Chapter 9

Sleep and Biological Rhythms

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Learning Objectives

What Is Sleep?

LO 9.1 Describe the progression, behaviors, and EEG characteristics of sleep stages.

LO 9.2 Explain the patterns of brain activity in REM and slow-wave sleep.

Why Do We Sleep?

LO 9.3 Suggest some possible functions of sleep.

LO 9.4 Compare the roles of slow-wave and REM sleep in learning.

Physiological Mechanisms of Sleep and Waking

LO 9.5 Explain how adenosine contributes to regulating sleep.

LO 9.6 Describe how acetylcholine, norepinephrine, serotonin, histamine, and orexin contribute to regulating arousal.

LO 9.7 Summarize factors involved in regulating transitions between sleep and waking.

LO 9.8 Describe the flip-flop circuit in neural control of transition to REM.

Disorders of Sleep

LO 9.9 Describe the symptoms, treatment, and biological basis of insomnia.

LO 9.10 Describe the symptoms, treatment, and biological basis of narcolepsy.

LO 9.11 Describe the symptoms, treatment, and biological basis of REM sleep behavior disorder.

LO 9.12 Describe the symptoms, treatment, and biological basis of bedwetting, sleepwalking, and night terrors.

Biological Clocks

LO 9.13 List examples of circadian rhythms and zeitgebers.

LO 9.14 Identify the role of the suprachiasmatic nucleus in regulating circadian rhythms, and explain how the clock mechanism functions.

LO 9.15 Describe how melatonin regulates seasonal rhythms.

LO 9.16 Explain why shift work and jet lag result in changes of circadian rhythms.

Lately, Miguel felt anxious about going to bed because of the unpleasant experiences he had been having. Several times in the past few months, while lying in bed waiting to fall asleep, he felt as if he were paralyzed. It was a really strange feeling. A couple of times he woke up just before it was time for his alarm to go off and again felt unable to move. Then the alarm would ring, and he would quickly shut it off.

His dreams had also become more intense in a disturbing way. One night brought the worst experience of all. As Miguel was falling asleep, he felt again as if he were paralyzed. Then he saw his former roommate enter his bedroom—but that wasn't possible! Since the time he graduated from college he had lived alone, and he always locked the door. He tried to say something, but he couldn't. His roommate was holding a hammer. He walked up to the bed, stood over Miguel, and suddenly raised the hammer, as if to hit his head. When Miguel awoke in the morning, he shuddered in fear. It had seemed so real! It must have been a dream, but he didn't think he was asleep.

That same day at the office, he had trouble concentrating on his work. He forced himself to review his notes, because he had to present the details of a new project to the board of directors. This was his big chance; if the project were accepted, he would certainly be chosen to lead it, and that would mean a promotion and a raise. Naturally, with so much at stake, he was nervous when he entered the boardroom. His boss introduced Miguel and asked him to begin. Miguel glanced at his notes and opened his mouth to talk. Suddenly, he felt his knees buckle. All his strength seemed to slip away. He fell heavily to the floor. He could hear people running over and asking what had happened. He couldn't move anything except his eyes. His boss asked, "Miguel, are you all right?" Miguel looked at his boss and tried to answer, but he couldn't speak. A few seconds later, he felt his strength coming back. He opened his mouth and said, "I'm okay." He struggled to his knees and then sat in a chair, feeling weak and frightened.

"You have a condition known as narcolepsy," said the doctor whom Miguel visited after his experience in the boardroom. "It's a problem that concerns the way your brain controls sleep. I'll have you spend a night in the sleep clinic and get some recordings done to confirm this diagnosis. You told me that lately you've been taking short naps during the day. What were these naps like? Were you suddenly struck by an urge to sleep?"

Miguel nodded. "I just had to put my head on the desk, even though I was afraid that my boss might see me. But I don't think I slept more than five minutes or so."

"Did you still feel sleepy when you woke?"

"No," he replied, "I felt fine again."

The doctor nodded. "All the symptoms you describe—the sleep attacks, the paralysis you experienced before sleeping and after waking up, the fainting spell you had today—they all fit together. Fortunately, we can usually control narcolepsy with medication. There is no reason why you can't continue with your job. If you'd like, I can talk with your boss and reassure her, too."

Miguel's story illustrates several aspects of sleep that will be explored in more depth throughout this chapter. Sleep is a complex behavior that involves many regions of the brain. The regulation of sleep and waking cycles is an intricate balance between activity in neural circuits, the actions of hormones, and environmental factors. As you read this chapter, consider the different aspects of sleep represented in Miguel's case, from an intense motivation to sleep, to visual hallucination, to muscle paralysis. Miguel's experience even prompts a very basic question: Why do we sleep at all?

In the first two modules, we will describe what is known about sleep and why we do it. In the third module, we will describe the search for the chemicals and the neural circuits that control sleep and wakefulness. In the fourth module, we examine sleep disorders. In the final module, we discuss the brain's biological clock—the mechanism that controls daily rhythms of sleep and wakefulness.

What Is Sleep?

Sleep is a behavior. That statement might seem unusual, because we often think of behaviors as activities that involve movements, such as walking or talking. Except for the rapid eye movements in a particular stage, sleep is not distinguished by movement. What characterizes sleep is that the insistent urge of sleepiness (a motivation) forces us to seek out a quiet, warm, comfortable place; lie down; and remain there for several hours (a behavior). Because we remember very little about what happens while we sleep, it can be easy to think of sleep more as a change in consciousness than as a behavior.

electromyogram (EMG) (*my oh gram*) An electrical potential recorded from an electrode placed on or in a muscle.

electro-oculogram (EOG) (*ah kew loh gram*) An electrical potential from the eyes, recorded by means of electrodes placed on the skin around them; detects eye movements.

alpha activity Smooth electrical activity of 8–12 Hz recorded from the brain; generally associated with a state of relaxation.

beta activity Irregular electrical activity of 13–30 Hz recorded from the brain; generally associated with a state of arousal.

Stages of Sleep

LO 9.1 Describe the progression, behaviors, and EEG characteristics of sleep stages.

The best research on human sleep is conducted in a sleep laboratory. A sleep laboratory, usually located at a university or medical center, typically has one or several small bedrooms near an observation room, where the researcher or technician spends the night (trying to stay awake). The sleeper will be prepared for electrophysiological measurements by attaching electrodes to the scalp to monitor the brain's activity with an *electroencephalogram* (EEG),

and to the face to monitor muscle activity with an **electromyogram (EMG)**. Electrodes attached around the eyes monitor eye movements, recorded as the **electro-oculogram (EOG)**. In addition, other electrodes and transducing devices can be used to monitor autonomic measures such as heart rate, respiration, and changes in the ability of the skin to conduct electricity. (See Figure 9.1.)

When a person is awake, an EEG typically shows two basic patterns of activity: *alpha activity* and *beta activity*. **Alpha activity** consists of regular, medium-frequency waves of 8–12 Hz (hertz, which measures cycles per second). The brain produces this activity when a person is resting quietly. Although alpha waves sometimes occur when a person's eyes are open, they are much more prevalent when they are closed. The other type of waking EEG pattern, **beta activity**, consists of irregular, mostly low-amplitude waves of 13–30 Hz. In an EEG, amplitude describes the height of a wave. Beta activity shows *desynchrony* and reflects the fact that many different neural circuits in the brain are actively processing information. Desynchronized activity occurs when a person is alert and paying attention to events in the environment or is thinking actively

EEG electrodes record from many neurons all at once, reporting on the sum of their electrical activity. If the cells are active at about the same time, their electrical messages are synchronized and appear as a large, clear wave in the EEG data. If they are active at random, their electrical messages are desynchronized and appear as small, chaotic waveforms without a clear pattern. Imagine that all of the neurons in a particular cortical region are swimmers in a pool. These swimmers are all making waves by pushing the water with their hands. When the swimmers are synchronized and all push together to make their individual waves, their waves combine to make one big wave moving across the pool. When the swimmers are desynchronized, each individual makes their own waves at random. Some of the small waves crash into each other and cancel out the progress of other waves. The pool is full of many small, chaotic individual waves moving in every direction, similar to the summed electrical activity of neurons that are active when beta activity is recorded. (See Figure 9.2.)

Researchers and physicians have carefully examined the EEG record of sleepers and identified particular patterns of waveform activity that correspond with different periods, or stages, of sleep. The current sleep scoring system identifies stages of wakefulness (stage W), three stages of non-REM sleep (NREM 1, 2, and 3) and one REM sleep stage (stage R) (Berry et al., 2012; Silber et al., 2007). (See Table 9.1.) You'll read more about REM later in this module.

Let's look at a typical night's sleep of a female college student in a sleep laboratory, using sleep stage scoring guidelines. (An experimenter would obtain similar results from a male, with one exception, which is noted later.) The experimenter attaches the electrodes, turns the lights off, and closes the door. Our volunteer becomes drowsy and soon enters stage 1 sleep, marked by the presence of some **theta activity** (3.5–7.5 Hz), which indicates that the firing of neurons in the neocortex is becoming more synchronized. This stage is actually a transition between sleep and wakefulness. If we watch our volunteer's eyelids, we will see that from time to time they slowly open and close and that her eyes roll upward and downward. During this time, the sleeper may experience *hypnic jerks*, muscle contractions followed by relaxation. Many people experience these along with a falling sensation. About 10 minutes later she enters stage 2 sleep. The EEG during this stage is generally irregular but contains periods of theta activity, *sleep spindles*, and *K complexes*. Sleep spindles are short bursts of waves of 12–14 Hz that occur between two and five times a minute during stages 1–3 of sleep. They appear to play a role in keeping individuals asleep, especially in response to external stimuli like sounds, and the consolidation of memories (Antony & Paller, 2017; Diekelmann & Born, 2010). Increased numbers of sleep spindles are correlated with increased scores on tests of intelligence (Fogel and Smith, 2011). K complexes are sudden, sharp waveforms, which, unlike sleep spindles, are usually found only during stage 2 sleep. They spontaneously occur at the rate of approximately one per minute but often can be triggered by noises—especially unexpected noises. K complexes appear before delta waves, which occur in the deepest levels of sleep. New research has begun to examine the creation and function of spindles and K complexes in the transition to deeper sleep stages (Ioannides et al., 2017).

Figure 9.1 Participant in a Sleep Study

Electrodes allow researchers to measure electrophysiological activity from the brain and muscles in the face and around the eyes.

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theta activity EEG activity of 3.5–7.5 Hz that occurs intermittently during early stages of slow-wave sleep and REM sleep.

Figure 9.2 Synchronous and Desynchronous EEG Activity

(a) If the cells are active at about the same time, their electrical messages are synchronized and appear as a large, clear wave in the EEG data. This is an example of synchronous delta activity. (b) If neurons are active at different times, their electrical messages are desynchronized and appear as small, chaotic waveforms without a clear pattern in the EEG data. This is an example of desynchronous beta wave activity.

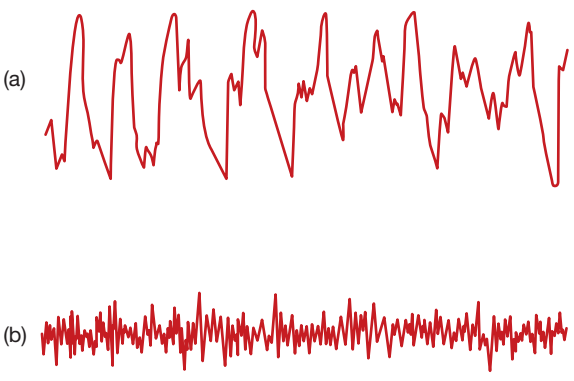


Table 9.1 Sleep Stages

(Based on: Silber et al., 2007 and Horne, J. A. Why we sleep: The functions of sleep in humans and other mammals. Oxford, England: Oxford University Press, 1988. REM=rapid eye movement; NREM=Non REM sleep)

Sleep Stages	Description	EEG Data
Waking	Alpha (8–12Hz) and beta (13–30Hz) activity	Awake Alpha activity Beta activity
Stage 1	NREM sleep, consists of theta activity (3.5–7.5Hz).	Stage 1 sleep Theta activity
Stage 2	NREM sleep, contains sleep spindles and K complexes	Stage 2 sleep Sleep spindle K complex Seconds
Stage 3	NREM sleep, consists of delta activity (<3.5Hz)	Delta activity
REM	REM sleep, consists of theta and beta activity	REM sleep Theta activity Beta activity

slow-wave sleep Non-REM sleep, characterized by synchronized EEG activity during its deeper stages.

delta activity Regular, synchronous electrical activity of less than 4 Hz recorded from the brain; occurs during the deepest stages of slow-wave sleep.

REM sleep A period of desynchronized EEG activity during sleep, at which time dreaming, rapid eye movements, and muscular paralysis occur; also called ***paradoxical sleep***.

The person is sleeping soundly now; but if awakened, she might report that she has not been asleep. About 15 minutes later, the volunteer enters **slow-wave sleep**, signaled by high-amplitude **delta activity** (less than 3.5 Hz) in stage 3 sleep. (Look again at Table 9.1.)

About 90 minutes after the beginning of sleep, there is an abrupt change in some of the physiological measures recorded from our volunteer. The EEG suddenly becomes mostly desynchronized, with occasional occurrences of theta waves, very similar to the record obtained during stage 1 sleep. (Refer back to Table 9.1.) We can also see that her eyes are rapidly moving back and forth beneath her closed eyelids. We can see this activity in the EOG, recorded from electrodes attached to the skin around her eyes, or we can observe the eye movements directly—the cornea produces a bump in the closed eyelids that allows us to see the eye movement directly. We also see that the EMG becomes silent. There is a loss of muscle tone. Aside from occasional twitching, a person actually becomes paralyzed during REM sleep. This peculiar stage of sleep is very different from the quiet sleep we saw earlier. It is referred to as *rapid eye movement sleep*, or ***REM sleep***.

By most criteria, stage 3 is the deepest stage of sleep. Only loud noises will wake a person in this stage, and when awakened, the person acts groggy and confused. In contrast, during REM sleep a person might not react to most noises, but he or she is easily aroused by meaningful stimuli, such as the sound of his or her name. Also, when awakened from REM sleep, a person appears alert and attentive.

If we wake our volunteer during REM sleep and ask her what was going on, she is likely to report that she was dreaming. The dreams of REM sleep tend to be narrative in form, with a storylike progression of events. On the other hand, if we wake her during slow-wave sleep and ask, "Were you dreaming?" she will most likely say, "No." However, if we question her more carefully, she might report a thought, an image, or some emotion.

During the rest of the night, our volunteer's sleep alternates between periods of REM and non-REM sleep. Each cycle is approximately 90 minutes long, containing a 20- to 30-minute period of REM sleep. An eight-hour sleep will contain typically four or five periods of REM sleep. Figure 9.3 shows a graph of a typical night's sleep. The vertical axis indicates the EEG activity that is being recorded. REM sleep and stage 1 sleep are placed on the same horizontal line because similar patterns of EEG activity occur in these stages.

Figure 9.3 A Typical Pattern of Sleep Stages During a Single Night

The dark blue shading in this figure represents REM sleep.

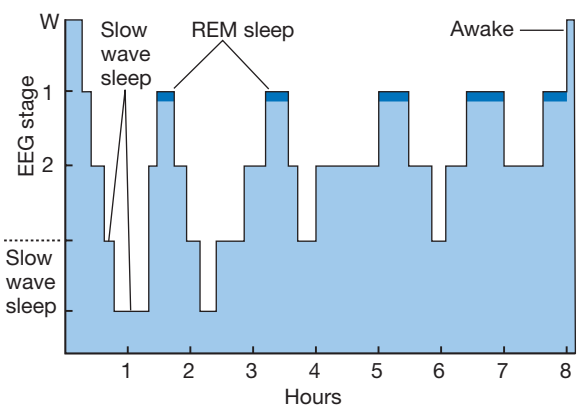


Table 9.2 Principal Characteristics of REM and Slow-Wave Sleep

REM Sleep	Slow-Wave Sleep
EEG desynchrony (rapid, irregular waves)	EEG synchrony (slow waves)
Lack of muscle tonus	Moderate muscle tonus
Rapid eye movements	Slow or absent eye movements
Penile erection or vaginal secretion	Lack of genital activity
Dreams	

Note that most slow-wave sleep occurs during the first half of the night. Later in the night, periods of non-REM sleep contain more and more stage 2 sleep, and periods of REM sleep (indicated by the horizontal bars) become longer.

REM sleep paralysis occurs because most of our spinal and cranial motor neurons are strongly inhibited. (The ones that control respiration and eye movements are not inhibited.) At the same time the brain is very active. Cerebral blood flow and oxygen consumption are accelerated. In addition, during most periods of REM sleep a male's penis and a female's clitoris will become at least partially erect, and a female's vaginal secretions will increase (Schmidt and Schmidt, 2004). However, in males, genital changes do not signify that the person is experiencing a dream with sexual content (Fisher et al., 1965). (People can have dreams with sexual content. In males some dreams culminate in ejaculation— the so-called nocturnal emissions, or "wet dreams." Females, too, experience orgasm during sleep.)

The important differences between REM sleep and slow-wave sleep are listed in Table 9.2.

Watch
STAGES OF SLEEP

Brain Activity During Sleep

LO 9.2 **Explain the patterns of brain activity in REM and slow-wave sleep.**

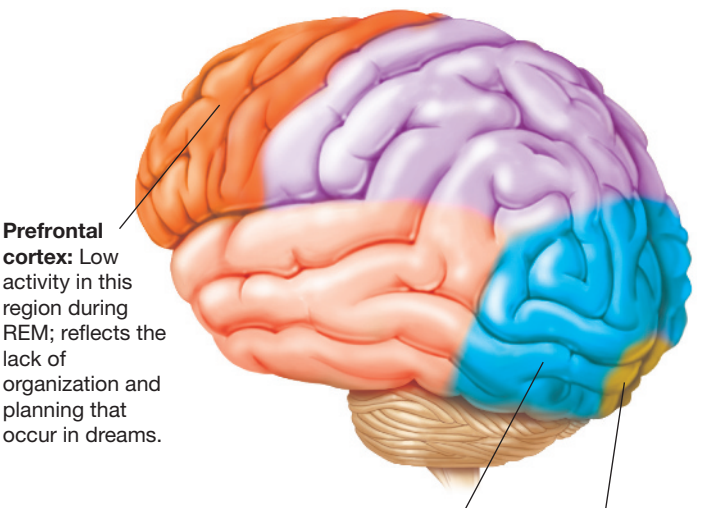
Although we do not respond very much to the environment while we are asleep, we are not unconscious. In the morning we usually forget what we experienced while asleep, so in retrospect, it can be easy to conclude that we were unconscious. However, the brain is very active in sleep. Next, we will explore this topic with a focus on what is known about brain activity in REM and slow-wave sleep.

BRAIN ACTIVITY IN REM AND DREAMING The rate of cerebral blood flow in the human brain during REM sleep is high in the extrastriate cortex (visual association cortex) but low in the striate (primary) visual cortex and the prefrontal cortex (Braun et al., 1998; Madsen et al., 1991). The lack of activity in the striate cortex makes sense because the (closed) eyes are not receiving visual input during sleep. The high level of activity in the extrastriate cortex likely reflects the visual hallucinations that occur during dreams. The prefrontal cortex is involved in making plans, keeping track of the organization of events in time, and distinguishing illusion from reality. Maybe you have even noticed this in your own experience. Have you ever had dreams where past, present, and future were interchanged, or the timing of events was unrealistic? (See Figure 9.4.)

Some people experience lucid dreaming, or an awareness that they are dreaming and are not awake. Some researchers have hypothesized that activation of the normally inactive prefrontal cortex during REM could be involved in the experience of lucid dreaming. Lucid dreaming may also occur in non-REM sleep.

Stumbrys et al. (2013) designed an interesting experiment to test the role of prefrontal cortex activity in lucid dreaming. The researchers recruited volunteers to spend three nights in a sleep research lab. On the first night, participants acclimated to the lab. On the second and third nights, a technique called transcranial direct current stimulation (tDCS) was used to apply a weak current

Figure 9.4 Striate, Extrastriate, and Prefrontal Cortex Activity in REM Sleep


Prefrontal cortex: Low activity in this region during REM; reflects the lack of organization and planning that occur in dreams.
Extrastriate cortex: High activity in this region during REM; reflects visual hallucinations during dreaming.
Striate cortex: Low activity in this region during REM due to lack of visual input.

to the scalp of participants to activate the dorsolateral prefrontal cortex on one night. On the other night participants received a sham activation. Participants were awakened after each REM episode and asked to report their dreams. Participants reported more lucid dreams in response to tDCS versus sham stimulation. Subsequent research has begun to identify more specific stimulation to produce lucid dreams using a similar technique, fronto-temporal transcranial alternating current stimulation (tACS; Voss et al., 2014). Although preliminary, these studies hint at the role of at least one brain region involved in REM lucid dreaming.

Eye movements made during REM sleep may be related to the visual imagery that occurs while we dream. Eye movements of a person while dreaming during REM sleep are similar to what would be expected if the person was actually watching an event while awake (Andrillion et al., 2015; Roffwarg et al., 1962). In addition, evidence indicates that the particular brain mechanisms active during a dream are those that would become active if the events in the dream were actually occurring. For example, cortical and subcortical motor mechanisms become active during a dream that contains movement (or would likely contain movement), as if the person were actually moving (McCarley and Hobson, 1979; De Carli et al., 2015). In addition, if a dream involves talking and listening, regions of the dreamer's brain that are involved in speaking and listening become especially active (Hong et al., 1996).

BRAIN ACTIVITY IN SLOW-WAVE SLEEP Although narrative, storylike dreaming and the associated brain activity most often occur during REM sleep, changes in brain activity can also accompany dreamlike imagery experienced during slow-wave sleep. Regional cerebral blood flow during slow-wave sleep is generally decreased throughout the brain compared to waking. However, some researchers have found localized increases in the visual and auditory cortexes, which are hypothesized to be the neural basis for the dreamlike imagery experienced during slow-wave sleep. Blood flow to the thalamus and cerebellum is decreased in slow-wave sleep (Hofle et al., 1997; Tüshaus et al., 2017).

Module Review What Is Sleep?

Thought Question

Some people report that they are "in control" of some of their dreams—that they feel as if they determine what comes next and are not simply swept along passively. Have you ever had this experience? Have you ever had a "lucid dream," in which you were aware of the fact that you were dreaming? Describe evidence for changes in brain activity associated with lucid dreaming.

Why Do We Sleep?

From past experience, you probably know how strong the urge to sleep can be and how uncomfortable it can feel when we have to resist it and stay awake. With the exception of the effects of severe pain and the need to breathe, sleepiness is probably the most insistent drive that we can experience. People can commit suicide by refusing to eat or drink, but not even the most determined person can defy the urge to sleep indefinitely. Sleep will come, sooner or later, no matter how hard a person tries to stay awake.

Earlier in the chapter, we posed the question "Why do we sleep?" Researchers have attempted to answer this question in a variety of ways. Although the issue is not yet settled, most researchers believe that the primary function of slow-wave sleep is to permit the brain to rest. In addition, slow-wave sleep and REM sleep promote different types of learning, and REM sleep appears to promote brain development too.

Functions of Sleep

LO 9.3 Suggest some possible functions of sleep.

Sleep is a universal phenomenon among vertebrates and appears to be essential for survival. As far as we know, all mammals and birds sleep (Durie, 1981). Reptiles also sleep, and

fish, amphibians, and even insects enter periods of quiescence that resemble sleep. However, only warm-blooded vertebrates (mammals and birds) exhibit clear REM sleep, with muscular paralysis, EEG signs of desynchrony, and rapid eye movements. Birds such as flamingos, which sleep while perched on one leg, do not lose tone in the muscles they use to remain standing. Also, animals such as moles, which move their eyes very little while awake, show few signs of eye movement while asleep.

EFFECTS OF SLEEP DEPRIVATION What happens when you miss several hours, or a whole night, of sleep? On one hand, missing one night of sleep is not fatal and so we know that while important, we are able to survive and function (reasonably well) despite occasional lost sleep.

On the other hand, if we look more closely, several cognitive functions are disrupted by even one night of sleep deprivation. Extended sleep loss amplifies these effects. People's cognitive abilities are typically affected by sleep loss, especially on tasks that require attention or vigilance (Lim and Dinges, 2010). Regular or extensive sleep deprivation is also associated with adverse health outcomes, including weight gain and obesity, diabetes, hypertension, heart disease and stroke, depression, impaired immune function, increased pain, greater risk of accidents and even increased risk of death. Extreme sleep loss can even be fatal (more on this at the end of the section). In response to accumulating evidence about the negative impact of sleep deprivation, the current recommendation from a panel of sleep research experts is that adults should sleep seven or more hours per night on a regular basis to promote optimal health (Watson et al., 2015).

What happens to sleep-deprived individuals after they sleep again? Most of them sleep longer the next night or two, but they never regain all of the sleep they lost. In one remarkable case a 17-year-old boy stayed awake for 264 hours to earn a place in the Guinness Book of World Records (Gulevich et al., 1966). After his sleep deprivation, the boy slept for a little less than 15 hours and reported feeling fine. He slept slightly more than 10 hours the second night and just under nine hours the third. Almost 67 hours of missing sleep were never made up. However, percentages of recovery were not equal for all stages of sleep. Only 7 percent of stages 1 and 2 were made up, but 68 percent of slow-wave sleep and 53 percent of REM sleep were made up. Other studies have found similar results, suggesting that slow-wave sleep and REM sleep are prioritized over the other stages (Kales et al., 1970).

In studies of sleep deprivation in rats, extensive sleep deprivation is even fatal (Rechtschaffen and Bergmann, 1995, 2002; Rechtschaffen et al., 1983, 1989). The cause of death is still not understood. The rats' brains appeared to be normal, and there were no obvious signs of inflammation or damage to other internal organs. The animals' levels of stress hormones were not unusually high, so the deaths could not be attributed to simple stress. If they were given a high-calorie diet to compensate for their increased metabolic rate, the rats lived longer, but eventually they succumbed (Everson and Wehr, 1993). As we will see later in this chapter, damage to parts of the basal forebrain causes insomnia, and if the animals do not recover from their sleeplessness, they die.

An inherited neurological disorder called **fatal familial insomnia** results in damage to portions of the thalamus (Gallassi et al., 1996; Montagna et al., 2003; Sforza et al., 1995). The symptoms of this disease include deficits in attention and memory, followed by a dreamlike, confused state; loss of control of the autonomic nervous system and the endocrine system; increased body temperature; and insomnia. The first signs of sleep disturbances are reductions in sleep spindles and K complexes. As the disease progresses, slow-wave sleep completely disappears, and only brief episodes of REM sleep (without the accompanying paralysis) remain. As the name indicates, the disease is fatal. Whether the insomnia, caused by the brain damage, contributes to the other symptoms and to the patient's death is not known.

Schenkein and Montagna (2006a, 2006b) describe the case of a man diagnosed with a form of fatal familial insomnia that usually causes death within 12 months. Because several relatives had died of this disorder, the man knew what to expect, and he enlisted the aid of several physicians to administer drugs and treatments designed to help him sleep. For several months the treatments did help him to sleep, and the man survived about a year longer than would have been expected, with a higher quality of life during the course of his illness. Further studies will be needed to determine whether his increased survival time was a direct result of the increased sleep.

fatal familial insomnia A fatal inherited disorder characterized by progressive insomnia.

The available evidence suggests that the brain needs to rest periodically to recover from adverse side effects of its waking activity. But what is the nature of these adverse effects? Siegel (2005) suggests that among the waste products produced by the high metabolic rate associated with waking activity of the brain are free radicals, chemicals that contain at least one unpaired electron. Free radicals are highly reactive oxidizing agents; they can bind with electrons from other molecules and damage the cells in which they are found, a process known as oxidative stress. Prolonged sleep deprivation caused an increase in free radicals in the brains of rats and resulted in oxidative stress (Ramanathan et al., 2002). During slow-wave sleep, reduced metabolic rates permit restorative mechanisms in the cells to destroy the free radicals and prevent their damaging effects. Additional research suggests that sleep enhances the removal of other neurotoxins from the brain through the glymphatic system—connections between interstitial fluid surrounding cells and the CSF (Xie et al., 2013).

EFFECTS OF PHYSICAL ACTIVITY ON SLOW-WAVE SLEEP Sleep deprivation studies with humans suggest that the brain may need slow-wave sleep to recover from the day's physical activities. Another way to determine whether sleep is needed for restoration of physiological functioning is to look at the effects of daytime activity on nighttime sleep. If the function of sleep is to repair the effects on the body of physical activity during waking hours, then we should expect that sleep and exercise are related. We should sleep more after a day of vigorous exercise than after a day spent quietly at a desk or watching TV.

The relationship between sleep and exercise is probably subtle. Some early studies reported no changes in slow-wave or REM sleep of healthy participants who spent six weeks resting in bed (Ryback and Lewis, 1971) and little difference in the sleep of individuals with spinal injuries that produced physical paralysis, compared to control participants (Adey et al., 1968). On the other hand, epidemiological studies suggest a positive relationship between physical exercise and sleep quality and quantity (Youngstedt and Kline, 2006). A meta analysis of experimental studies reported that exercise interventions had a modest effect on measures of improved sleep quantity, increased time in stage two sleep, and reduced time in REM sleep (Youngstedt et al., 1997). In contrast, a study of college students comparing sleep on their most and least physically active days over a three and a half month period reported a minimal effect of exercise on sleep. There was no significant correlation between physical exercise and sleep in this sample, and exercising more than two additional hours per day only improved sleep efficiency about 1% (time asleep divided by time-in-bed; Youngstedt et al., 2003). Although sleep provides the body with rest, it seems unlikely that this is the primary overall function of sleep, including slow-wave sleep.

EFFECTS OF COGNITIVE ACTIVITY ON SLOW-WAVE SLEEP If the primary function of slow-wave sleep is to permit the brain to rest and recover from its daily cognitive activity, then we might expect that a person would spend more time in slow-wave sleep after a day of intense cerebral activity. Tasks that demand alertness and mental activity do increase glucose metabolism in the brain (Roland, 1984). The most significant increases are seen in the frontal lobes, where slow-wave activity is most intense during non-REM sleep (Huber et al., 2004). Other studies show that after a day of rigorous mental activity, (Horne and Minard, 1985) or several weeks of working memory training, (Pugin et al., 2015) slow-wave sleep increases.

FUNCTIONS OF REM SLEEP REM sleep is a time of intense physiological activity. The eyes dart about rapidly, the heart rate shows sudden accelerations and decelerations, breathing becomes irregular, and the brain becomes more active. It would be unreasonable to expect that REM sleep has the same functions as slow-wave sleep. An early report on the effects of REM sleep deprivation (Dement, 1960) observed that as the deprivation progressed, participants had to be awakened from REM sleep more frequently. It was as if the "pressure" to enter REM sleep built up. Furthermore, after several days of REM sleep deprivation, participants would show a **rebound phenomenon** when permitted to sleep normally; they spent a much greater-than-normal percentage of the recovery night in REM sleep. This rebound suggests that there is a need for a certain amount of REM sleep—that REM sleep is controlled by a regulatory mechanism. If selective deprivation causes a deficiency in REM sleep, the deficiency is made up later, when uninterrupted sleep is permitted.

rebound phenomenon The increased frequency or intensity of a phenomenon after it has been temporarily suppressed; for example, the increase in REM sleep seen after a period of REM sleep deprivation.

Researchers have long been struck by the fact that the highest proportion of REM sleep is seen during the most active phase of brain development in infancy and childhood. Perhaps, then, REM sleep plays a role in this process (Siegel, 2005). But if the function of REM sleep is to promote brain development, why do adults have *any* REM sleep? One possibility is that REM sleep facilitates the massive changes in the brain that occur during development but also some of the more modest changes responsible for learning that occur throughout the lifespan. As we will see in the next section, evidence does suggest that REM sleep facilitates learning—but so does slow-wave sleep.

Sleep and Learning

LO 9.4 Compare the roles of slow-wave and REM sleep in learning.

More than just allowing the brain to rest, sleep helps consolidate long-term memories (Marshall and Born, 2007). Slow-wave sleep and REM sleep play different roles in memory consolidation.

As we will see in Chapter 13, there are two major categories of long-term memory: declarative memory (also called explicit memory) and nondeclarative memory (also called implicit memory). Declarative memories are the ones that people can talk (or declare) about, such as memories of past episodes in their lives. They also include memories of the relationships between stimuli or events, such as the spatial relationships between landmarks we use to navigate around our environment. Nondeclarative memories include those gained through experience and practice that do not necessarily involve an attempt to "memorize" information, such as learning to drive a car, throwing and catching a ball, or recognizing a person's face. Research has found that slow-wave sleep and REM sleep play different roles in consolidating declarative and nondeclarative memories.

Let's explore evidence from two studies that examined the effects of a nap on memory consolidation. Mednick et al. (2003) had participants learn a nondeclarative visual discrimination task at 9:00 a.m. The participants' ability to perform the task was tested 10 hours later, at 7:00 p.m. Some of the participants took a 90-minute nap during the day between training and testing. The investigators recorded the EEGs of the sleeping participants to determine who experienced REM sleep. (All of them engaged in slow-wave sleep, because this stage of sleep always comes first in healthy people.) The investigators found that the performance of participants who did not take a nap was worse when they were tested at 7:00 p.m. than it had been at the end of training. The participants who engaged only in slow-wave sleep did about the same during testing as they had done at the end of training. However, the participants who engaged in REM sleep performed significantly better. Thus, REM sleep strongly facilitated the consolidation of a nondeclarative memory. (See Figure 9.5.)

In the second study, Tucker et al. (2006) trained participants on two tasks: a declarative task (learning a list of paired words) and a nondeclarative task (learning to trace a pencil-and-paper design while looking at the paper in a mirror). Afterward, some of the participants took a one-hour nap. Their EEGs were recorded, and they were awakened before they could engage in REM sleep. The participants' performance on the two tasks was then tested six hours after the original training. The researchers found that, compared with participants who stayed awake, a nap consisting of just slow-wave sleep increased the participants' performance on the declarative task but had no effect on the performance of the nondeclarative task. (See Figure 9.6.) So these two experiments (and many others we have not described) indicate that REM sleep facilitates consolidation of nondeclarative memories and that slow-wave sleep facilitates consolidation of declarative memories.

Peigneux et al. (2004) had participants learn their way around a computerized virtual-reality town. This task is very similar to what people do when they learn their way around a real town. They must learn the relative locations of landmarks and streets that connect them so that they can find particular locations when the experimenter places them at various starting points. As we will see in Chapter 13, the hippocampus plays an essential role in learning of this kind. Peigneux and his colleagues used functional brain imaging to measure regional

Figure 9.5 REM Sleep and Learning

Only after a 90-minute nap that included both slow-wave sleep and REM sleep was an improvement seen in the participants' performance on a nondeclarative visual discrimination task.

(Data from Mednick, S., Nakayama, K., & Stickgold, R. (2003). Sleep-dependent learning: a nap is as good as a night. *Nature Neuroscience*, 6(7), 697.)

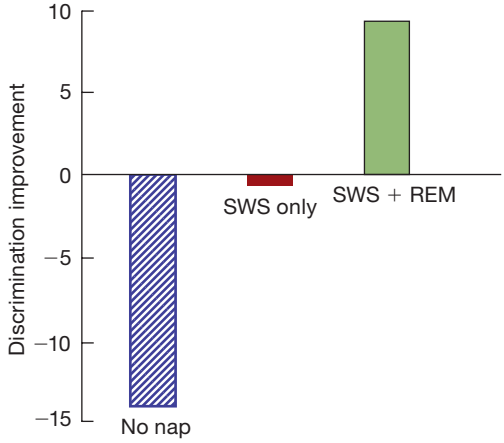


Figure 9.6 Slow-Wave Sleep and Learning

Participants learned a declarative learning task (list of paired words) and a nondeclarative learning task (mirror tracing). After a nap that included just slow-wave sleep, only participants who learned the declarative learning task showed improved performance, compared with participants who stayed awake.

(Data from Mednick, S., Nakayama, K., & Stickgold, R. (2003). Sleep-dependent learning: a nap is as good as a night. *Nature Neuroscience*, 6(7), 697.)

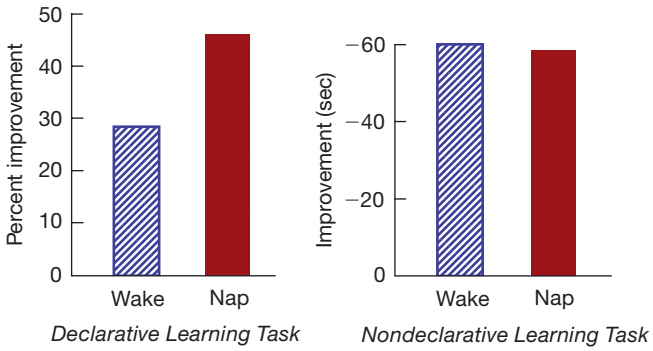
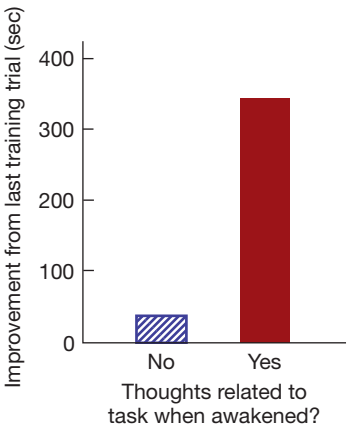


Figure 9.7 Thinking About Past Experiences While Asleep

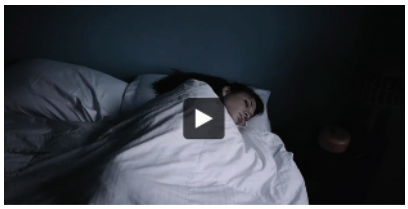
The graph shows superior performance of participants who, when awakened, reported having thoughts about a virtual reality navigation task they had been learning the previous day.

(Wamsley, E. J., Tucker, M., Payne, J. D., Benavides, J. A., & Stickgold, R. (2010). Dreaming of a learning task is associated with enhanced sleep-dependent memory consolidation. *Current Biology*, 20(9), 850–855.)



Watch

RESEARCH ON COLLEGE STUDENT SLEEP AND LEARNING



brain activity and found that the same regions of the hippocampus were activated during route learning and during slow-wave sleep the following night. These patterns were *not* seen during REM sleep.

Using a similar virtual reality navigation task, Wamsley et al. (2010) awakened participants from slow-wave sleep during an afternoon nap that followed training and asked them to report everything that they were thinking about. They found that participants whose thoughts were related to the task performed much better during a subsequent session on the navigation task than those who did not report such thoughts. Even though people who are awakened during slow-wave sleep seldom report narrative dreams, the sleeping brain rehearses information that was acquired during the previous period of wakefulness. (See Figure 9.7.)

Many studies with laboratory animals have directly recorded the activity of individual neurons in the animals' brains. These studies, too, indicate that the brain appears to rehearse newly learned information during slow-wave sleep (O'Neill et al., 2010). Chapter 13 reviews this evidence and describes research on the relevant brain mechanisms.

Module Review Why Do We Sleep?

Thought Question

In this module, you read about the roles of slow-wave sleep and REM sleep in performance on declarative and nondeclarative memory tasks. List some tasks from your own life that require you to use your declarative and nondeclarative memory. Imagine that you have just taught someone else how to perform these tasks. Using information from this module, recommend how your "student" could use a nap to their advantage in performing the task you have taught them.

Physiological Mechanisms of Sleep and Waking

So far, we have discussed the nature of sleep and its functions. Now it is time to examine what researchers have discovered about the physiological mechanisms that are responsible for the behavior of sleep and for its counterpart, alert wakefulness.

Neural Control of Sleep

LO 9.5 Explain how adenosine contributes to regulating sleep.

As we have seen, sleep is *regulated;* that is, if an organism is deprived of slow-wave sleep or REM sleep, the organism will make up at least part of the missed sleep when permitted to do so. In addition, the amount of slow-wave sleep that a person obtains during a daytime nap is deducted from the amount of slow-wave sleep he or she obtains the next night (Karacan et al., 1970). These facts suggest that some physiological mechanism monitors the amount of sleep that an organism needs to keep track of the sleep debt we incur during hours of wakefulness.

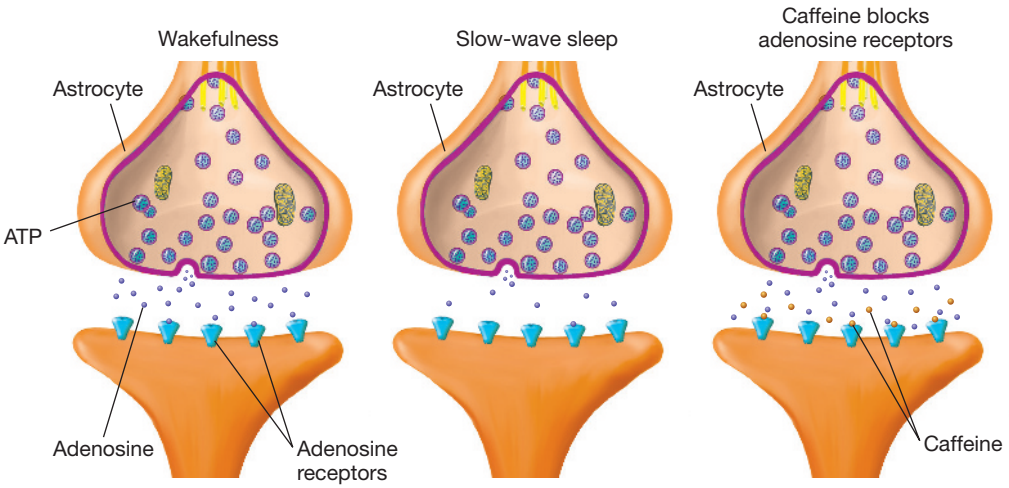
One explanation is that the body produces a sleep-promoting substance that accumulates during wakefulness and is destroyed during sleep. The longer someone is awake, the longer they have to sleep to deactivate this substance. If such a substance exists, it does not appear to be found in the general circulation of the body. The cerebral hemispheres of some species of animals can sleep at different times (Mukhametov, 1984). If sleep is controlled by chemicals in the blood, the hemispheres should sleep at the same time. This observation suggests that if sleep is controlled by chemicals, these chemicals are produced within the brain and act there. In support of this suggestion Oleksenko et al. (1992) obtained evidence that indicates that each hemisphere of the brain incurs its own sleep debt. The researchers deprived a bottlenose dolphin of sleep in only one hemisphere by waking the animal whenever that hemisphere entered a sleep state. When they allowed the animal to sleep normally, they saw a rebound of slow-wave sleep only in the deprived hemisphere.

Benington, Kodali, and Heller (1995) suggested that **adenosine**, a nucleoside neuromodulator, might play a primary role in the control of sleep, and subsequent studies have supported this suggestion. Astrocytes maintain a small stock of nutrients in the form of glycogen, an insoluble carbohydrate that is also stocked by the liver and the muscles. In times of increased brain activity, this glycogen is converted into fuel for neurons; thus, prolonged wakefulness causes a decrease in the level of glycogen in the brain (Kong et al., 2002). A fall in the level of glycogen causes an increase in the level of extracellular adenosine, which has an inhibitory effect on neural activity. This accumulation of adenosine serves as a sleep-promoting substance. During slow-wave sleep, neurons in the brain rest, and the astrocytes renew their stock of glycogen (Basheer et al., 2004; Wigren et al., 2007). If wakefulness is prolonged, even more adenosine accumulates, which inhibits neural activity and produces the cognitive and emotional effects that are seen during sleep deprivation. (As we saw in Chapter 4, caffeine blocks adenosine receptors to reduce sleepiness.) (See Figure 9.8.)

adenosine *(a den oh seen)* A neuromodulator that is released by neurons engaging in high levels of metabolic activity; may play a primary role in the initiation of sleep.

Figure 9.8 Adenosine Across Sleep/Waking Cycle

Astrocytes release ATP, which is converted to adenosine in the extracellular space. Adenosine accumulates during wakefulness and is reduced during slow-wave sleep. Caffeine blocks the adenosine receptors, preventing the inhibitory effect on neural activity and reducing the effects of sleep deprivation.



As you probably know, people differ in their sleep needs. Evidence suggests that genetic factors affect the typical duration of a person's slow-wave sleep. Rétey et al. (2005) discovered one of these factors—variability in the gene that encodes for an enzyme, *adenosine deaminase*, which is involved in the breakdown of adenosine. The investigators found that people with the G/A allele for this gene, which encodes for a form of the enzyme that breaks down adenosine more slowly, spent approximately thirty minutes more time in slow-wave sleep than did people with the more common G/G allele. Levels of adenosine in people with the G/A allele decreased more slowly during slow-wave sleep, and as a consequence the slow-wave sleep of these people was prolonged. The role of adenosine as a sleep-promoting factor is discussed in more detail in the following section.

Neural Control of Arousal

LO 9.6 **Describe how acetylcholine, norepinephrine, serotonin, histamine, and orexin contribute to regulating arousal**

As you've seen, sleep consists of several different stages with different characteristics. The waking state, too, is nonuniform. Sometimes we are alert and attentive, and sometimes we fail to notice much about what is happening around us. Sleepiness has an effect on wakefulness. If we are fighting to stay awake, the struggle might impair our ability to concentrate on other things. But everyday observations suggest that even when we are not sleepy, our alertness can vary. For example, when we observe something very interesting (or frightening or simply surprising), we become more alert and aware of our surroundings.

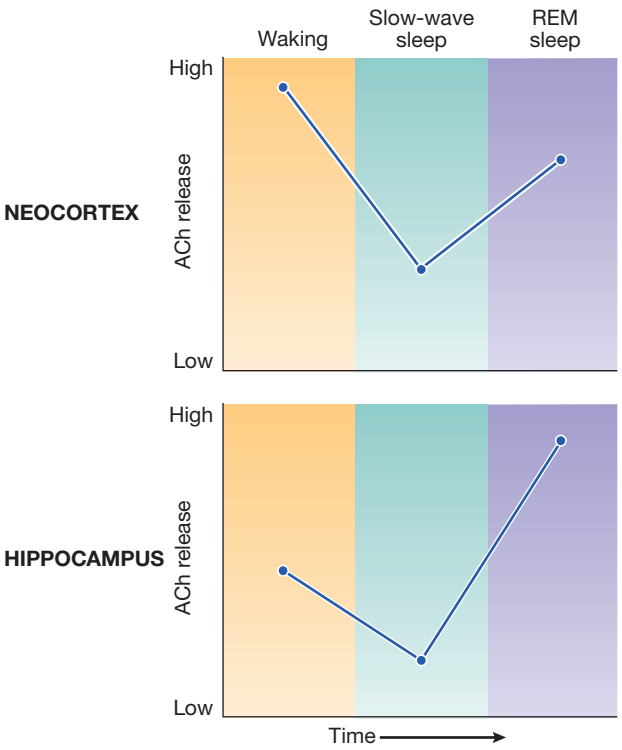
locus coeruleus (*sa roo lee us*) A dark-colored group of noradrenergic cell bodies located in the pons near the rostral end of the floor of the fourth ventricle; involved in arousal and vigilance.

Circuits of neurons that secrete at least five different neurotransmitters play a role in some aspect of an animal's level of alertness and wakefulness—what is commonly called *arousal*: acetylcholine, norepinephrine, serotonin, histamine, and orexin.

Figure 9.9 Acetylcholine and the Sleep/Waking Cycle

Acetylcholine is released from the cortex and hippocampus.

(Data from Marrosu, F., Portas, C., Mascia, M. S., Casu, M. A., Fà, M., Giagheddu, M.,... & Gessa, G. L. (1995). Microdialysis measurement of cortical and hippocampal acetylcholine release during sleep-wake cycle in freely moving cats. *Brain Research*, 671(2), 329–332.)



ACETYLCHOLINE One key neurotransmitter involved in arousal—especially of the cerebral cortex—is acetylcholine (ACh). Two groups of acetylcholinergic neurons, one in the pons and one in the basal forebrain, produce activation and cortical desynchrony when they are stimulated (Jones, 1990; Steriade, 1996). A third group of acetylcholinergic neurons, located in the medial septum, controls the activity of the hippocampus.

Researchers have long known that acetylcholinergic agonists increase EEG signs of cortical arousal and that acetylcholinergic antagonists decrease them (Vanderwolf, 1992). Marrosu et al. (1995) used microdialysis probes to measure the release of acetylcholine in the hippocampus and neocortex, two regions whose activity is closely related to an animal's alertness and behavioral arousal. They found that the levels of ACh in these regions were high during both waking and REM sleep— periods during which the EEG displayed desynchronized activity—but low during slow-wave sleep. (See Figure 9.9.)

NOREPINEPHRINE Investigators have long known that catecholamine agonists such as amphetamine produce arousal and sleeplessness. These effects appear to be mediated primarily by the noradrenergic system of the **locus coeruleus** (LC), located in the dorsal pons. Neurons of the locus coeruleus give rise to axons that branch widely, releasing norepinephrine (from axonal varicosities) throughout the neocortex, hippocampus, thalamus, cerebellar cortex, pons, and medulla; thus, they potentially affect widespread and important regions of the brain.

Aston-Jones and Bloom (1981) recorded the activity of noradrenergic neurons of the LC across the sleep/waking cycle in rats. They found that this activity was closely related to behavioral arousal: The firing rate of these neurons was high during wakefulness, low during slow-wave sleep, and almost zero during REM sleep. Within a few seconds of awakening, the rate of firing increased dramatically. (See Figure 9.10.)

Many researchers believe that activity of noradrenergic LC neurons increases an animal's vigilance—its ability to pay attention to stimuli in the environment (Aston-Jones et al., 1994).

SEROTONIN A third neurotransmitter, serotonin (5-HT), also appears to play a role in activating behavior. Almost all of the brain's serotonergic neurons are found in the **raphe nuclei**, which are located in the medullary and pontine regions of the reticular formation. The axons of these neurons project to many parts of the brain, including the thalamus, hypothalamus, basal ganglia, hippocampus, and neocortex. Stimulation of the raphe nuclei causes locomotion and cortical arousal (as measured by the EEG), whereas PCPA, a drug that prevents the synthesis of serotonin, reduces cortical arousal (Peck and Vanderwolf, 1991).

Figure 9.11 shows the activity of serotonergic neurons, recorded by Trulson and Jacobs (1979). As you can see, these neurons, like the noradrenergic neurons studied by Aston-Jones and Bloom (1981), were most active during waking. Their firing rate declined during slow-wave sleep and became virtually zero during REM sleep. However, once the period of REM sleep ended, the neurons temporarily became very active again.

HISTAMINE The fourth neurotransmitter implicated in the control of wakefulness and arousal is histamine. You may already be aware that antihistamines, which are used to treat allergies, can cause drowsiness. They do so by blocking histamine H_2 receptors in the brain. More modern antihistamines cannot cross the blood–brain barrier, so they do not cause drowsiness.

The cell bodies of histaminergic neurons are located in the **tuberomammillary nucleus (TMN)** of the hypothalamus, located at the base of the brain just rostral to the mammillary bodies. The axons of these neurons project primarily to the cerebral cortex, thalamus, basal ganglia, basal forebrain, and other regions of the hypothalamus. The projections to the cerebral cortex directly increase cortical activation and arousal, and projections to acetylcholinergic neurons of the basal forebrain and dorsal pons do so indirectly, by increasing the release of acetylcholine in the cerebral cortex (Brown et al., 2001; Khateb et al., 1995). The activity of histaminergic neurons is high during waking, but low during slow-wave sleep and REM sleep (Steininger et al., 1996). In addition, injections of drugs that prevent the synthesis of histamine or block histamine H_1 receptors decrease waking and increase sleep (Lin et al., 1998). Also, infusion of histamine into the basal forebrain region of rats causes an increase in waking and a decrease in non-REM sleep (Ramesh et al., 2004).

Figure 9.10 Norepinephrine and the Sleep/Waking Cycle

This graph shows the activity of noradrenergic neurons in the locus coeruleus of freely moving rats during various stages of sleeping and waking.

(Aston-Jones, G., & Bloom, F. E. (1981). Activity of norepinephrine-containing locus coeruleus neurons in behaving rats anticipates fluctuations in the sleep-waking cycle. *Journal of Neuroscience*, 1(8), 876–886.)

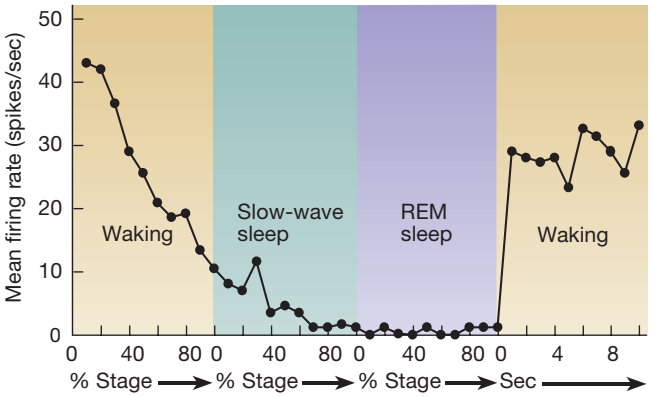
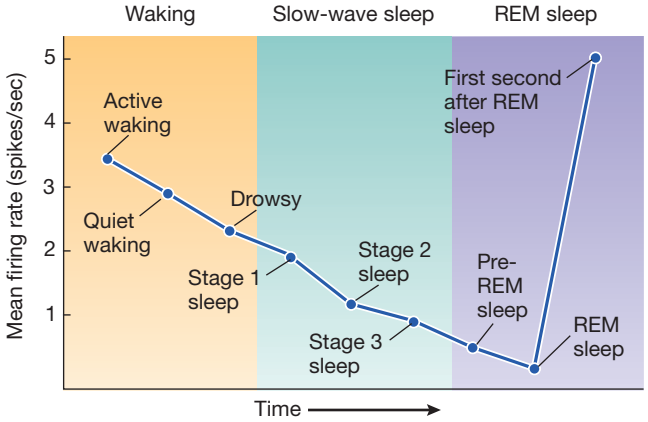


Figure 9.11 Serotonin and the Sleep/Waking Cycle

This graph shows the activity of serotonergic (5-HT secreting) neurons in the dorsal raphe nuclei of freely moving cats during various stages of sleep and waking.

(Trulson, M. E., & Jacobs, B. L. (1979). Raphe unit activity in freely moving cats: correlation with level of behavioral arousal. *Brain Research*, 163(1), 135–150.)



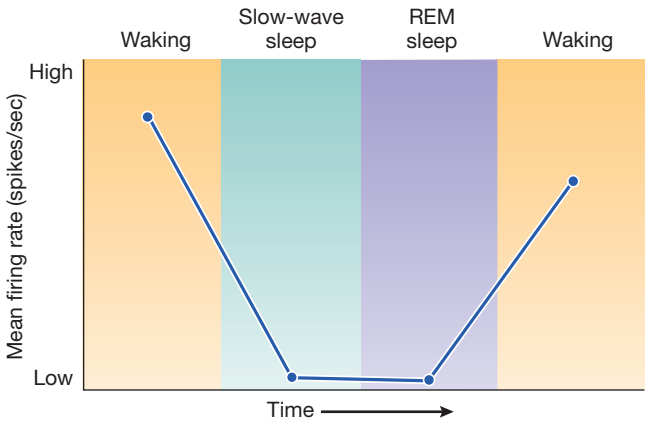
raphe nuclei (*ruh fay*) A group of nuclei located in the reticular formation of the medulla, pons, and midbrain, situated along the midline; contain serotonergic neurons.

tuberomammillary nucleus (TMN) A nucleus in the ventral posterior hypothalamus, just rostral to the mammillary bodies; contains histaminergic neurons involved in cortical activation and behavioral arousal.

Figure 9.12 Orexin, Histamine, and the Sleep/Waking Cycle

Orexin and histamine follow the same pattern during various stages of sleeping and waking.

(Based on Mileykovskiy, B. Y., Kiyashchenko, L. I., & Siegel, J. M. (2005). Behavioral correlates of activity in identified hypocretin/orexin neurons. *Neuron*, 46(5), 787–798.)



OREX IN The lateral hypothalamus contains the cell bodies of all of the neurons that secrete the peptide **orexin** (also known as *hypocretin*). The axons of these neurons project to almost every part of the brain, including the cerebral cortex and all of the regions involved in arousal and wakefulness, including the locus coeruleus, raphe nuclei, tuberomammillary nucleus, and acetylcholinergic neurons in the dorsal pons and basal forebrain (Sakurai, 2007). Orexin has an excitatory effect in all of these regions.

Mileykovskiy et al. (2005) recorded the activity of single orexinergic neurons in unanesthetized rats and found that the neurons fired at a high rate during alert or active waking and at a low rate during quiet waking, slow-wave sleep, and REM sleep. The highest rate of firing was seen when the rats were engaged in exploratory activity. (See Figure 9.12.)

Adamantidis et al. (2010) used genetic transfer to insert ChR2 protein into orexinergic neurons of the lateral hypothalamus of mice. They found that optogenetic activation of these neurons with blue light awakened the animals from either REM or non-REM sleep.

Narcolepsy is most often treated with modafinil, a drug that suppresses the drowsiness associated with this disorder. Ishizuka et al. (2010) found that the alerting effects of modafinil are exerted by stimulating the release of orexin in the TMN, which activates the histaminergic neurons located there (see Table 9.3).

Neural Control of Sleep/Waking Transitions

LO 9.7 **Summarize factors involved in regulating transitions between sleep and waking.**

What controls the transition between sleep and waking? The following sections will explore homeostatic, allostatic, and circadian factors, as well as the roles of the preoptic area, and orexin in controlling sleep/waking transitions.

HOMEOSTATIC, ALLOSTATIC, AND CIRCADIAN FACTORS The level of brain activity is largely controlled by the five sets of arousal neurons described in the previous section. A high level of activity of these neurons keeps us awake, and a low level puts us to sleep. The control of sleep is *homeostatic* in nature, and follows the principles that regulate our eating and drinking, which are described in Chapter 12. But under some conditions, it is important for us to stay awake—for example, when we are being threatened by a dangerous situation. The conscious attempt to control our sleep is *allostatic* in nature, a term that refers to reactions to stressful events in the environment (danger, lack of water, and so on) that serve to override homeostatic control. Allostatic control is mediated primarily by hormonal and neural responses to stressful situations (described in Chapter 11) and by neuropeptides (such as orexin) that are involved in hunger and thirst. Finally, *circadian* factors, or time of day factors, tend to restrict our period of sleep to a particular portion of the day/night cycle. (Circadian control of sleep cycles is described in the last module of this chapter.)

orexin A peptide, also known as ***hypocretin,*** produced by neurons whose cell bodies are located in the hypothalamus; their destruction causes narcolepsy.

Table 9.3 Summary of Neurochemical Levels Involved in Regulation of the Sleep/Waking Cycle

Chemical	Brain Region containing cell bodies	Waking Levels	SWS Levels	REM Levels
Adenosine	-	Increase with longer periods of wake	Low	Low
Acetylcholine	Pons, basal forebrain, medial septum	High	Low	High
Norepinephrine	Locus coeruleus	High	Low	Low
Serotonin	Raphe nuclei	High	Decreasing	Low
Histamine	Tuberomammillary nucleus	High	Low	Low
Orexin	Lateral hypothalamus	High	Low	Low

THE PREOPTIC AREA What controls the activity of the arousal neurons? The *preoptic area*, a region of the anterior hypothalamus, is the brain region most involved in the initiation of sleep. The preoptic area contains neurons whose axons form inhibitory synaptic connections with the brain's arousal neurons. When our preoptic neurons (let's call them *sleep neurons*) become active, they suppress the activity of our arousal neurons, and we fall asleep (Saper, Scammell, and Lu, 2005).

The majority of the sleep neurons are located in the **ventrolateral preoptic area (vlPOA)**. In addition, some are located in the nearby *median preoptic nucleus (MnPN)*. Damage to vlPOA neurons suppresses sleep (Lu et al., 2000), and the activity of these neurons, measured by their levels of Fos protein, increases during sleep. Experiments have shown that the sleep neurons secrete the inhibitory neurotransmitter GABA and that they send their axons to the five brain regions involved in arousal described in the previous section (Gvilia et al., 2006; Sherin et al., 1998; Suntsova et al., 2007). As we saw, activity of neurons in these five regions causes cortical activation and behavioral arousal. Inhibition of these regions, then, is a necessary condition for sleep.

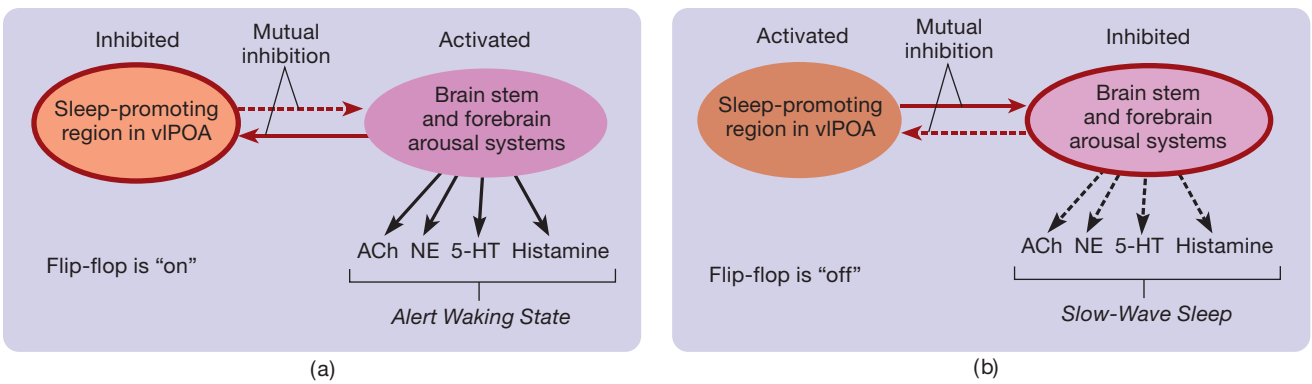
Flip-flop Circuits For Sleep/wake Transitions The sleep neurons in the preoptic area receive inhibitory inputs from some of the same regions they inhibit, including the tuberomammillary nucleus, raphe nuclei, and locus coeruleus (Chou et al., 2002); thus, they are inhibited by histamine, serotonin, and norepinephrine. As Saper and his colleagues (Saper et al., 2001; Saper et al., 2010) suggest, this mutual inhibition may provide the basis for establishing periods of sleeping and waking. They note that reciprocal inhibition also characterizes an electronic circuit known as a *flip-flop*. A flip-flop can assume one of two states, usually referred to as on or off—or 0 or 1 in computer applications. Thus, either the sleep neurons are active and inhibit the wakefulness neurons, or the wakefulness neurons are active and inhibit the sleep neurons. Because these regions are mutually inhibitory, it is impossible for neurons in both sets of regions to be active at the same time. In fact, sleep neurons in the vlPOA are silent until an animal shows a transition from waking to sleep (Takahashi et al., 2009). (See Figure 9.13.)

Stability in Flip-flop Circuits A flip-flop has an important advantage: When it switches from one state to another, it does so quickly. Clearly, it is most advantageous to be either asleep or awake; a state that has some of the characteristics of both sleep and wakefulness would be maladaptive. However, there is one problem with flip-flops: They can be unstable. In fact, people with narcolepsy and animals with damage to the orexinergic system of neurons exhibit just this characteristic. They have great difficulty remaining awake when nothing interesting is happening, and they have trouble remaining asleep for an extended

ventrolateral preoptic area (vlPO A) A group of GABAergic neurons in the preoptic area whose activity suppresses alertness and behavioral arousal and promotes sleep.

Figure 9.13 The Sleep/Waking Flip-Flop

According to Saper et al. (2001), the major sleep-promoting region (the vlPOA) and the major wakefulness-promoting regions (the basal forebrain and pontine regions that contain acetylcholinergic neurons; the locus coeruleus, which contains noradrenergic neurons; the raphe nuclei, which contain serotonergic neurons; and the tuberomammillary nucleus of the hypothalamus, which contains histaminergic neurons) are reciprocally connected by inhibitory GABAergic neurons. (a) When the flip-flop is in the "wake" state, the arousal systems are active and the vlPOA is inhibited, and the animal is awake. (b) When the flip-flop is in the "sleep" state, the vlPOA is active and the arousal systems are inhibited, and the animal is asleep.



amount of time. (They also show intrusions of the characteristics of REM sleep at inappropriate times. We will discuss this phenomenon in the next section.)

Saper et al. (2001, 2010) suggest that an important function of orexinergic neurons is to help stabilize the sleep/waking flip-flop through their excitatory connections to the wakefulness neurons. Activity of this system of neurons tips the activity of the flip-flop toward the waking state, thus promoting wakefulness and inhibiting sleep. Perhaps your success at staying awake in a boring lecture depends on maintaining a high rate of firing of your orexinergic neurons, which would keep the flip-flop in the waking state. (See Figure 9.14.) A mathematical model of the sleep/waking flip-flop constructed by Rempe et al. (2010) confirmed the role of orexigenic neurons in stabilizing the circuit.

ROLE OF OREXIN IN SLEEP/WAKING TRANSITIONS Orexin-releasing neurons are involved in all three factors that control sleep and wakefulness: homeostatic, allostatic, and circadian. During the waking part of the day/night cycle, orexinergic neurons receive an excitatory signal from the biological clock that controls rhythms of sleep and waking (*circadian factor*). These neurons also receive signals from brain mechanisms that monitor the animal's nutritional state. Hunger-related signals activate orexinergic neurons, and satiety-related signals inhibit them. In this way, orexinergic neurons maintain arousal during the times when an animal should search for food (*homeostatic factor*). Finally, orexinergic neurons receive inhibitory input from the vlPOA, which means that sleep signals that arise from the accumulation of adenosine can eventually overcome excitatory input to orexinergic neurons, and sleep can occur (*allostatic factor*). (See Figure 9.15.)

Neural Control of Transition to REM

LO 9.8 Describe the flip-flop circuit in neural control of transition to REM.

REM sleep is controlled by a flip-flop similar to the one that controls cycles of sleep and waking. The sleep/waking flip-flop determines when we wake and when we sleep. Once we fall asleep, a second REM flip-flop controls our cycles of REM sleep and slow-wave sleep. Once we fall asleep, the activity of orexinergic neurons ceases, which removes one source of the excitatory input to the REM-OFF region. As sleep progresses, the activity of

Figure 9.14 Role of Orexinergic Neurons in Sleep

The schematic diagram shows the effect of activation of the orexinergic system of neurons of the lateral hypothalamus on the sleep/waking flip-flop. Motivation to remain awake or events that disturb sleep activate the orexinergic neurons.

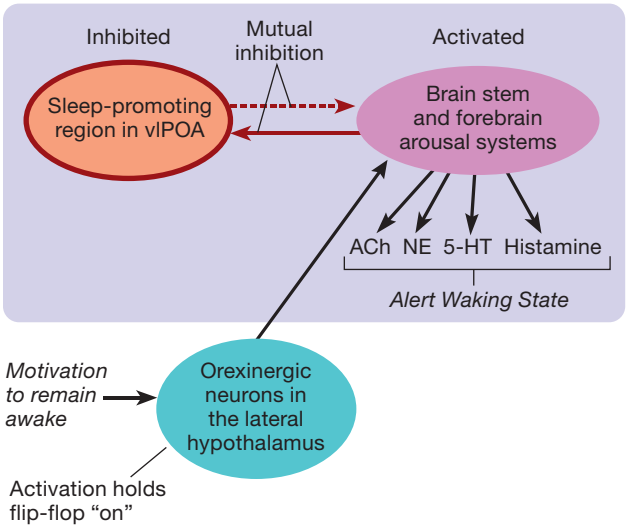
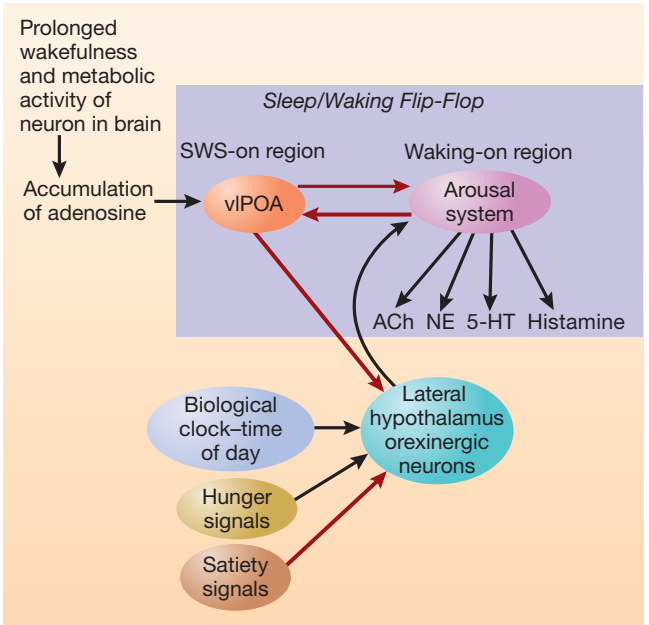


Figure 9.15 Homeostatic, Allostatic, and Circadian Factors influence the Sleep/Waking Flip-Flop

This figure shows the role of adenosine, time of day, and hunger and satiety signals on the sleep/waking flip-flop.



noradrenergic and serotonergic neurons gradually decreases. As a consequence, more of the excitatory input to the REM-OFF region is removed. The REM flip-flop tips to the on state, and REM sleep begins.

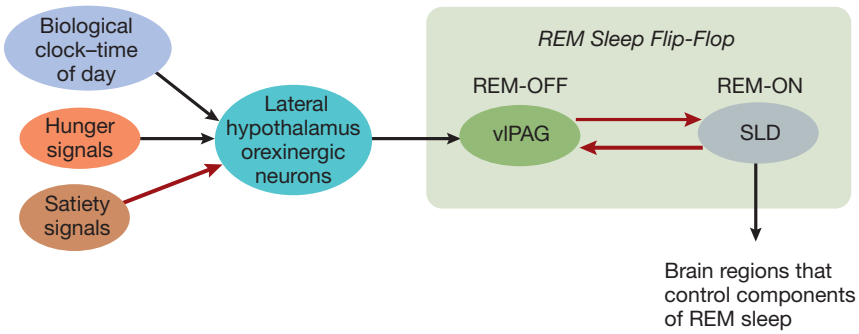
REM-ON neurons are found in a region of the dorsal pons, called the **sublaterodorsal nucleus (SLD)**. These cells fire at a high rate during REM. REM-OFF neurons are found in a region of the **ventrolateral periaqueductal gray matter (vlPAG)**. The REM-ON and REM-OFF regions are interconnected by means of inhibitory GABAergic neurons. Stimulating the REM-ON neurons produced REM sleep, while stimulating the REM-OFF neurons suppressed REM sleep (Fort et al., 2009; Saper et al., 2010). (See Figure 9.16.)

Activity of the REM flip-flop is involved in narcolepsy, REM muscle paralysis and rapid eye movements, and genital activity in REM. Degeneration of orexogenic neurons in narcolepsy destabilizes the REM flip-flop, making it easier to tip the REM flip-flop into the on state—even during waking—resulting in an attack of cataplexy. The REM flip-flop is responsible for ensuring muscle paralysis and rapid eye movements during REM. When the REM flip-flop tips to the on state, motor neurons in the spinal cord become inhibited and cannot respond to the signals arising from the motor cortex in the course of a dream. Damage to the REM-ON region removes the motor inhibition, and the individual physically acts out his or her dreams, instead of experiencing muscle paralysis during REM sleep. This is a symptom of REM behavior disorder, described later in this chapter. Neurons in the REM-ON region also send axons to regions of the thalamus that are involved in the control of cortical arousal, which may at least partly account for the EEG activation that is seen during REM sleep. Finally, REM-ON neurons initiate a series of neural excitation responsible for controlling rapid eye movement (Webster and Jones, 1988) and genital activity in REM (Salas et al., 2007; Schmidt et al., 2000).

sublaterodorsal nucleus (SLD) A region of the dorsal pons, just ventral to the locus coeruleus, that forms the REM-ON portion of the REM sleep flip-flop.

ventrolateral periaqueductal gray matter (vlPAG) A region of the dorsal midbrain that forms the REM-OFF portion of the REM sleep flip-flop.

Figure 9.16 The REM Sleep Flip-Flop



Module Review Physiological Mechanisms of Sleep and Waking

Thought Question

Have you ever been lying in bed, almost asleep, when you suddenly thought of something important you had forgotten to do? Did you then suddenly become fully awake and alert? If so, neurons in your brain's arousal systems likely became active, which aroused your cerebral cortex. What do you think the source of this activation was? What activated the arousal systems?

Disorders of Sleep

Because we spend about one-third of our lives sleeping, sleep disorders can have a significant impact on our quality of life. They can also affect the way we feel while we are awake.

Insomnia

LO 9.9 **Describe the symptoms, treatment, and biological basis of insomnia.**

Insomnia is a problem that affects approximately 25 percent of the population occasionally and 9 percent regularly (Ancoli-Israel and Roth, 1999). *Primary insomnia* is characterized as difficulty falling asleep after going to bed or after awakening during the night. *Secondary insomnia* is an inability to sleep due to another mental or physical condition, such as pain, substance use, or a psychological or neurological condition.

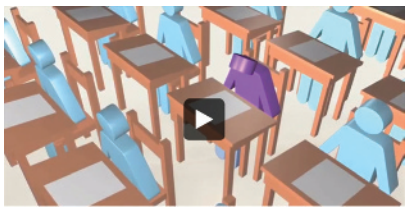
A significant problem in identifying insomnia is the challenge of self-reports. Most patients who receive a prescription for a sleeping medication are given one on the basis of their own description of their symptoms. Relatively few patients are observed during a night's sleep in a sleep laboratory. Studies on the sleep of people who report insomnia show that many people underestimate the amount of time they actually sleep. For example, Rosa and Bonnet (2000) found no differences in time spent sleeping between a group of people that did or did not report insomnia.

Many people experience a sleep-deprived state not because they suffer from insomnia but because the demands of their daily schedules lead them to stay up late or get up early (or both), resulting in less than the optimal amount of sleep. Chronic sleep deprivation can lead to serious health problems, including increased risk of obesity, diabetes, and cardiovascular disease (Orzel-Gryglewska, 2010).

TREATMENT Pharmacological and nonpharmacological interventions can be effective for treating insomnia. Nonpharmacological interventions include cognitive behavior therapy (CBT), progressive relaxation techniques, and changes in sleep hygiene. Sleep hygiene recommendations include maintaining a consistent sleep schedule (e.g., waking up and going to sleep at the same time each day), and keeping bedrooms dark, quiet, and cool. Pharmacological interventions include zolpidem (Ambien) or zaleplon (Sonata) which are agonists at the GABA receptor and part of a class of drugs known as the *hypnotics*. Benzodiazepines and over-the-counter antihistamines such as diphenhydramine are also used to treat insomnia (Benca, 2014). These drugs can produce side effects such as sleepiness or difficulty concentrating the following day. Chronic use of sleep-promoting drugs can lead to tolerance and *rebound insomnia* (a return and increase in insomnia) when their use is ended.

Watch

INSOMNIA AND SLEEP APNEA



SLEEP APNEA Patients with **sleep apnea** fall asleep and then stop breathing. Nearly all people, especially people who snore, have occasional episodes of sleep apnea, but not to the extent that it interferes with sleep. During a period of sleep apnea the level of carbon dioxide in the blood stimulates chemoreceptors (neurons that detect the presence of certain chemicals), and the person wakes up, gasping for air. The oxygen level of the blood returns to normal, the person falls asleep, and the whole cycle begins again. Because sleep is disrupted, people with this disorder typically feel sleepy and groggy during the day. Fortunately, many cases of sleep apnea are caused by an obstruction of the airway that can be corrected surgically or relieved by a device that attaches to the sleeper's face and provides pressurized air that keeps the airway open (Piccirillo et al., 2000; Sher, 1990).

sleep apnea (*app nee a*) Cessation of breathing while sleeping.

Narcolepsy

LO 9.10 **Describe the symptoms, treatment, and biological basis of narcolepsy.**

Narcolepsy is a neurological disorder characterized by sleep (or some of its components) at inappropriate times (Nishino, 2007). The symptoms include sleep attacks, cataplexy, and sleep paralysis and are the result of changes in the orexin system.

narcolepsy (*nahr ko lep see*) A sleep disorder characterized by periods of irresistible sleep, attacks of cataplexy, sleep paralysis, and hypnagogic hallucinations.

sleep attack A symptom of narcolepsy; an irresistible urge to sleep during the day, after which the person awakens feeling refreshed.

cataplexy (*kat a plex ee*) A symptom of narcolepsy; complete paralysis that occurs during waking.

SLEEP ATTACKS The primary symptom of narcolepsy is the **sleep attack**. In narcolepsy, a sleep attack is an overwhelming urge to sleep that can happen at any time but occurs most often under monotonous, boring conditions. Sleep generally lasts for 2–5 minutes. The person usually wakes up feeling refreshed.

CATAPLEXY Another symptom of narcolepsy—perhaps the most striking one—is **cataplexy**. During a cataplectic attack, a person will experience varying amounts of muscle weakness. In some cases the person will become completely paralyzed and slump down

to the floor. The person will lie there, fully conscious, for a few seconds to several minutes. In this situation, one of the phenomena of REM sleep—muscular paralysis—occurs at an inappropriate time. This loss of muscle tone is caused by massive inhibition of motor neurons in the spinal cord. When this happens during waking, the person loses control of his or her muscles. As in REM sleep, the person continues to breathe and is able to control eye movements.

Cataplexy is usually precipitated by strong emotional reactions or by sudden physical effort. Laughter, anger, or an effort to catch a suddenly thrown object can trigger a cataplectic attack. Miguel, the man described in the opener to this chapter, had his first cataplectic attack when he was addressing the board of directors of the company he worked for. Wise (2004) notes that patients with narcolepsy often try to avoid thoughts and situations that are likely to evoke strong emotions because they know that these emotions are more likely to trigger cataplectic attacks.

SLEEP PARALYSIS REM sleep paralysis sometimes intrudes into waking, such as just before or just after normal sleep. This symptom of narcolepsy is referred to as **sleep paralysis**, an inability to move just before the onset of sleep or on waking in the morning. A person can be snapped out of sleep paralysis by being touched or by hearing someone call his or her name. Sometimes, the mental components of REM sleep intrude into sleep paralysis as well. For example, a person might dream while lying awake, paralyzed. These episodes, called **hypnagogic hallucinations**, are often alarming or even terrifying. In the case study at the beginning of the chapter, Miguel experienced a hypnagogic hallucination and thought that his former roommate was trying to attack him.

PHYSIOLOGICAL BASIS OF NARCOLEPSY Fortunately, human narcolepsy is relatively rare, with an incidence of approximately one in 2,000 people. This hereditary disorder appears to involve a gene found on chromosome 6, but it is strongly influenced by unknown environmental factors (Mahowald and Schenck, 2005; Mignot, 1998; Nishino, 2007).

Years ago, researchers began a program to maintain breeds of dogs that are afflicted with narcolepsy, with the hopes that discovery of the causes of canine narcolepsy would further our understanding of the causes of human narcolepsy. Eventually, this research paid off. Lin et al. (1999) discovered that a mutation of a specific gene is responsible for canine narcolepsy. The product of this gene is a receptor for orexin. There are two orexin receptors, A and B. Lin and his colleagues discovered that the mutation responsible for canine narcolepsy involves the orexin-B receptor. Other research demonstrated that mutating the gene for orexin (Chemelli et al., 1999) or damaging orexinergic neurons (Gerashchenko et al., 2001, 2003) produces symptoms of narcolepsy.

In humans, narcolepsy appears to be caused by a hereditary autoimmune disorder. Most patients with narcolepsy are born with orexinergic neurons, but during adolescence the immune system attacks these neurons, and the symptoms of narcolepsy begin (Fontana et al., 2010).

TREATMENT The symptoms of narcolepsy can be treated with drugs. Sleep attacks can be diminished by stimulants such as methylphenidate (Ritalin), a catecholamine agonist (Vgontzas and Kales, 1999). Modafinil, another stimulant drug, is widely used to treat narcolepsy (Fry, 1998; Nishino, 2007). (Miguel, the man discussed in the opener to this chapter, takes this drug.) The REM sleep phenomena (cataplexy, sleep paralysis, and hypnagogic hallucinations) can be alleviated by antidepressant drugs, which facilitate both serotonergic and noradrenergic activity (Hublin, 1996; Mitler, 1994).

Key Concepts

A CLOSER LOOK AT NARCOLEPSY

REM Sleep Behavior Disorder

LO 9.11 Describe the symptoms, treatment, and biological basis of REM sleep behavior disorder.

REM sleep is typically accompanied by muscle paralysis. Although neurons in the motor cortex and subcortical motor systems are extremely active during REM sleep (McCarley and Hobson, 1979), people are unable to move at this time. (The occasional twitches that are

sleep paralysis A symptom of narcolepsy; paralysis occurring just before a person falls asleep.

hypnagogic hallucination (*hip na gah jik*) A symptom of narcolepsy; vivid dreams that occur just before a person falls asleep; accompanied by sleep paralysis.

seen during REM sleep are apparently signs of intense activity of motor neurons that are not completely suppressed.) The fact that people are paralyzed while they dream suggests the possibility that, if not for the paralysis, they would act out their dreams. In **REM sleep behavior disorder**, the behavior of people with this disorder corresponds with the contents of their dreams in REM. Consider the following case:

> "I was a halfback playing football, and after the quarterback received the ball from the center he lateraled it sideways to me and I'm supposed to go around the end and cut back over tackle and—this is very vivid—as I cut back over tackle there is this big 280-pound tackle waiting, so I, according to football rules, was to give him my shoulder and bounce him out of the way. . . when I came to I was standing in front of our dresser and I had [gotten up out of bed and run and] knocked lamps, mirrors and everything off the dresser, hit my head against the wall and my knee against the dresser." (Schenck et al., 1986, p. 294)

Like narcolepsy, REM sleep behavior disorder appears to be a neurodegenerative disorder with at least some genetic component (Schenck et al., 1993). It is often associated with neurodegenerative disorders such as Parkinson's disease (Boeve et al., 2007). The symptoms of REM sleep behavior disorder are the opposite of those of cataplexy. Instead of exhibiting paralysis outside REM sleep, patients with REM sleep behavior disorder fail to exhibit paralysis during REM sleep. As you might expect, drugs used to treat the symptoms of cataplexy will worsen the symptoms of REM sleep behavior disorder (Schenck and Mahowald, 1992). REM sleep behavior disorder is usually treated by clonazepam, a benzodiazepine (Aurora et al., 2010; Frenette, 2010)

Problems Associated with Slow-Wave Sleep

LO 9.12 Describe the symptoms, treatment, and biological basis of bedwetting, sleepwalking, and night terrors.

Some maladaptive behaviors occur during slow-wave sleep. These behaviors include bedwetting (*nocturnal enuresis*), sleepwalking (*somnambulism*), and night terrors (*pavor nocturnus*). All three events occur most frequently in children. Often bedwetting can be cured by training methods, such as having a special electronic circuit ring a bell when the first few drops of urine are detected in the bed sheet (a few drops usually precede the ensuing flood). Night terrors consist of anguished screams, trembling, a rapid pulse, and usually no memory of what caused the terror. Night terrors and somnambulism usually resolve as the child gets older. Neither of these phenomena is related to REM sleep; a sleepwalking person is not acting out a dream. Especially when it occurs in adulthood, sleepwalking appears to have a genetic component (Hublin et al., 1997).

REM sleep behavior disorder A neurological disorder in which the person does not become paralyzed during REM sleep and thus acts out dreams.

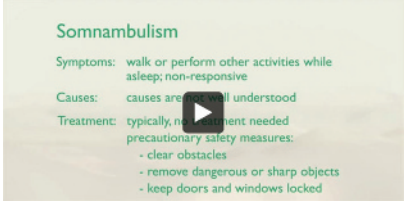
sleep-related eating disorder A disorder in which the person leaves his or her bed and seeks out and eats food while sleepwalking, usually without a memory for the episode the next day.

Sometimes, people can engage in complex behaviors while sleepwalking. Consider the following cases:

> One evening Ed Weber got up from a nap on the sofa, polished off a half-gallon of chocolate chip ice cream, then dozed off again. He woke up an hour later and went looking for the ice cream, summoning his wife to the kitchen and insisting, to her astonishment, that someone else must have eaten it.
>
> ***
>
> Talk show host Montel Williams reported his experience of eating raw meat from his refrigerator while asleep, not realizing **he** had eaten it, and asking *'Who ate my lunch meat?'* (Boodman, 2004, p. HE01)

Watch

SLEEP WALKING



Schenck et al. (1991) reported 19 cases of people with histories of eating during the night while they were asleep, which they labeled **sleep-related eating disorder**. Almost half of the patients had become overweight from night eating. Once patients realize that they are eating in their sleep, they often employ stratagems such as keeping their food under lock and key or setting alarms that will awaken them when they try to open their refrigerator.

Sleep-related eating disorder usually responds well to dopaminergic agonists or topiramate, an antiseizure medication, and may be provoked by zolpidem, a benzodiazepine agonist that has been used to treat insomnia (Howell and Schenck, 2009). An increased incidence of nocturnal eating in family members of people with this disorder suggests that heredity may play a role (De Ocampo et al., 2002).

Module Review Disorders of Sleep

Thought Question

Suppose you were spending the night at a friend's house and, hearing a strange noise during the night, got out of bed and found your friend walking around, still asleep. How would you tell whether your friend was sleepwalking or had REM sleep behavior disorder?

Biological Clocks

Much of our behavior follows regular rhythms. For example, we saw that the stages of sleep are organized around a 90-minute cycle of REM and slow-wave sleep. Our daily pattern of sleep and waking follows a 24-hour cycle. Finally, many animals display seasonal rhythms in which reproductive behaviors and hormone levels show yearly fluctuations. In recent years investigators have learned much about the neural mechanisms that are responsible for these rhythms.

Circadian Rhythms and Zeitgebers

LO 9.13 List examples of circadian rhythms and zeitgebers.

Daily rhythms in behavior and physiological processes are found throughout the plant and animal world. These cycles are generally called **circadian rhythms**. (*Circa* means "about," and *dies* means "day"; therefore, a circadian rhythm is one with a cycle of approximately 24 hours.) Some of these rhythms are passive responses to changes in illumination. However, other rhythms are controlled by mechanisms within the organism—by "internal clocks." For example, Figure 9.17 shows the activity of a rat during various conditions of illumination. Each horizontal line represents 24 hours. Black lines indicate the time the rat spends in wakefulness. Remember, rats are nocturnal animals, active at night. Actual records from a rat would show more variability and some short periods of waking during the day and perhaps some catnaps (ratnaps?) during the night. The upper portion of the figure shows the activity of the rat during a normal day/night cycle, with alternating 12-hour periods of light and dark.

Next, the light/dark cycle was shifted. The dark portion of the cycle now began four hours earlier. The animal's activity cycle quickly followed the change. (See the middle portion of Figure 9.17.) Finally, dim lights were left on continuously. The cyclical pattern in the rat's activity remained. Because there were no cycles of light and dark in the rat's environment, the source of rhythmicity must be located within the animal and the animal must possess an internal, biological clock. You can see that the rat's clock was not set precisely to 24 hours. When the illumination was held constant, the clock ran a bit slow. The animal began its period of activity approximately one hour later each day. (See the bottom portion of Figure 9.17.)

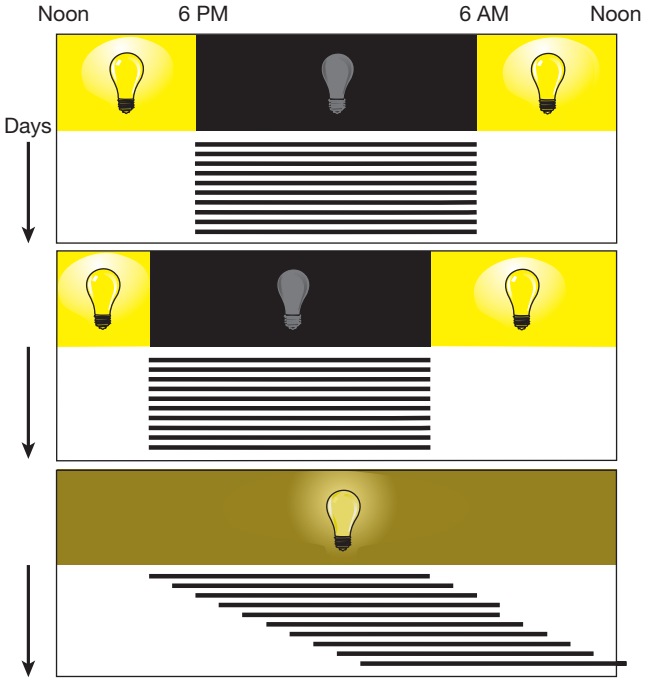
circadian rhythm (*sur kay dee un* or *sur ka dee un*) A daily rhythmical change in behavior or physiological process.

The phenomenon illustrated in Figure 9.17 is typical of the circadian rhythms shown by many species. A free-running clock, with a cycle of approximately 25 hours, controls some biological functions—in this case, sleep and wakefulness. Regular daily variation in the level of illumination (that is, sunlight and darkness) normally keeps the clock adjusted to 24 hours. Light serves as a **zeitgeber** (German for "time giver") and synchronizes the endogenous rhythm. Studies with many species of animals have shown that if they are maintained

zeitgeber (*tsite gay ber*) A stimulus (usually the light of dawn) that resets the biological clock that is responsible for circadian rhythms.

Figure 9.17 Wheel-Running Activity of a Rodent

Top: The animal's activity occurs at "night" (that is, during the 12 hours the light is off). Middle: The period of waking follows the new dark period when the light cycle is changed. Bottom: When the animal is maintained in constant dim illumination, it displays a free-running activity cycle of approximately 25 hours, which means that its period of waking begins about 1 hour later each day. The horizontal bars represent the portion of the light/dark cycle that the animal is active.



in constant darkness (or constant dim light), a brief period of bright light will reset their internal clock, advancing or slowing it depending on when the light flash occurs (Aschoff, 1979). For example, if an animal is exposed to bright light soon after dusk, the biological clock is set back to an earlier time—as if dusk had not yet arrived. On the other hand, if the light occurs late at night, the biological clock is set ahead to a later time—as if dawn had already come. Using zeitgebers such as clocks or other time cues, individuals who are blind or live in polar regions with extended periods of light or dark easily adapt to a 24-hour environment.

Humans also exhibit circadian rhythms, but without the benefits of modern civilization we would probably go to sleep earlier and get up earlier than we do because we use artificial lights to delay our bedtime and window shades to extend our time for sleep. Under constant illumination our biological clocks will run free, gaining or losing time like a watch that runs too slow or too fast. Different people have different cycle lengths, but most people in that situation will begin to live a "day" that is approximately 25 hours long. This works out quite well, because the morning light, acting as a zeitgeber, simply resets the clock.

The Suprachiasmatic Nucleus

LO 9.14 Identify the role of the suprachiasmatic nucleus in regulating circadian rhythms, and explain how the clock mechanism functions.

What brain regions might be involved in maintaining circadian rhythms? A specific region of the hypothalamus, called the **suprachiasmatic nucleus (SCN)**, receives light information from the environment and uses it to entrain behaviors to a 24-hour light/dark cycle.

ROLE IN CIRCADIAN RHYTHMS Researchers discovered that the primary biological clock of the rat is located in the SCN (Moore and Eichler, 1972; Stephan and Zucker, 1972); they found that lesions of the SCN disrupt daily patterns of wheel running, drinking, and hormonal secretion. The SCN also provides the primary control over the timing of sleep cycles. Rats are nocturnal animals; they sleep during the day and forage and feed at night. Lesions of the SCN abolish this pattern; sleep occurs in bouts randomly dispersed throughout both day and night (Ibuka and Kawamura, 1975; Stephan and Nuñez, 1977). However, rats with SCN lesions still obtain the same amount of sleep that normal animals do. The lesions disrupt the circadian control of sleep but do not affect its homeostatic control.

Because light is the primary zeitgeber for most mammals' activity cycles, we would expect that the SCN receives input from the visual system. Indeed, anatomical studies have revealed a direct projection from the retina to the SCN: the *retinohypothalamic pathway* (Aronson et al., 1993; Hendrickson et al., 1972). (See Figure 9.18.)

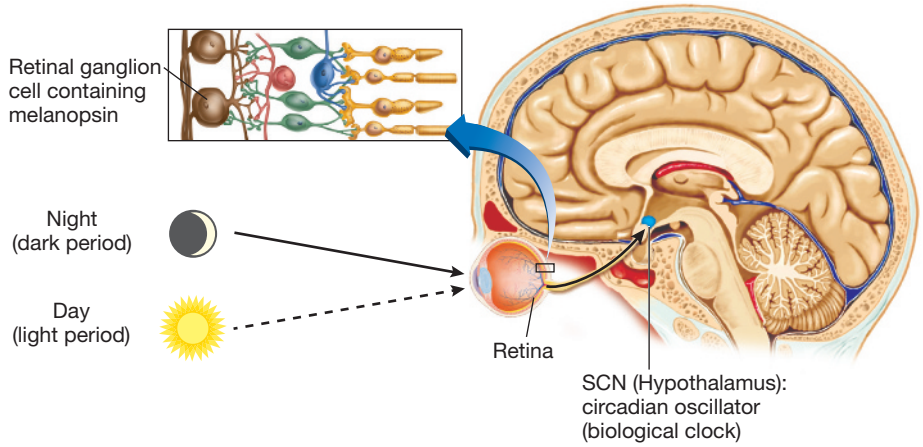
The photoreceptors in the retina that provide photic information to the SCN are neither rods nor cones—the cells that provide us with the information used for visual perception. Freedman et al. (1999) found that targeted mutations against genes necessary for production of both rods and cones did not disrupt the synchronizing effects of light. However, when they removed the mice's eyes, these effects were disrupted. These results suggested that there is a special photoreceptor that provides information about the ambient level of light that synchronizes circadian rhythms. Provencio et al. (2000) found the photochemical responsible for this effect, which they named **melanopsin**.

Unlike the other retinal photopigments, which are found in rods and cones, melanopsin is present in ganglion cells—the neurons whose axons transmit information from the eyes to the rest of the brain. Melanopsin-containing ganglion cells are sensitive to light, and their axons terminate in the SCN and in a region of the tectum involved in the pupils' response to light (Berson, Dunn, and Takao, 2002; Hattar et al., 2002).

suprachiasmatic nucleus (SCN) (*soo pra ky az mat ik*) A nucleus situated atop the optic chiasm. It contains a biological clock that is responsible for organizing many of the body's circadian rhythms.

melanopsin (*mell a nop sin*) A photo pigment present in ganglion cells in the retina whose axons transmit information to the SCN, the thalamus, and the olivary pretectal nuclei.

Figure 9.18 The Retinohypothalamic Pathway



Because the synchronizing effects of light on the SCN are mediated by specialized ganglion cells and not by rods and cones, people who have become blind because of loss of these photoreceptors can still show normal circadian rhythms. Although they cannot see, the melanopsin-containing ganglion cells in their retinas can still detect changes in light levels and synchronize the activity of their SCN.

SUPRACHIASMATIC NUCLEUS CONTROL OF SLEEP AND WAKING How does the SCN control cycles of sleep and waking? Efferent axons of the SCN responsible for organizing cycles of sleep and waking terminate in the *subparaventricular zone* (SPZ), a region just dorsal to the SCN (Deurveilher and Semba, 2005). Lu et al. (2001) found that excitotoxic lesions of the ventral part of the SPZ disrupted circadian rhythms of sleep and waking. The ventral SPZ projects to the *dorsomedial nucleus of the hypothalamus* (DMH), which in turn projects to several brain regions, including two that play critical roles in the control of sleep and waking: the vlPOA and the orexinergic neurons of the lateral hypothalamus. The projections to the vlPOA are inhibitory and thus inhibit sleep, whereas the projections to the orexinergic neurons are excitatory and thus promote wakefulness (Saper et al., 2005). The activity of these connections varies across the day/night cycle. In diurnal animals (such as ourselves) the activity of these connections is high during the day and low during the night. (See Figure 9.19.)

Although connections of SCN neurons with the SPZ play a critical role in circadian control of sleep and waking, several experiments suggest that the SCN can also control these rhythms by secretion of chemicals that diffuse through the brain's extracellular fluid (Lehman et al., 1987; Silver et al., 1996). Evidence suggests that the chemical signal may be a *prokineticin 2* (PK2), a protein contained in a subset of SCN neurons (Zhang et al., 2009). Presumably, the chemicals secreted by cells in the SCN affect rhythms of sleep and waking by diffusing into the SPZ and binding with receptors on neurons located there. In fact, Hu et al. (2007) found that mice with a targeted mutation against the PK2 gene showed disrupted circadian rhythms.

THE NATURE OF THE CLOCK All clocks must have a time base that makes them "tick." Mechanical clocks use flywheels or pendulums; electronic clocks use quartz crystals. The SCN, too, must contain a physiological mechanism that parses time into units. After years of research, investigators are finally beginning to understand the nature of the biological clock in the SCN.

What causes this intracellular ticking in SCN cells? Circadian rhythms in the SCN are produced as protein production rises to a certain level in the cell. When this maximal level is reached, the high concentration of protein in the cell turns off its own production through a negative feedback loop. As a result, the levels of the protein begin to decline, removing the inhibition, starting the production cycle again.

Key Concepts

CIRCADIAN RHYTHMS IN THE SCN

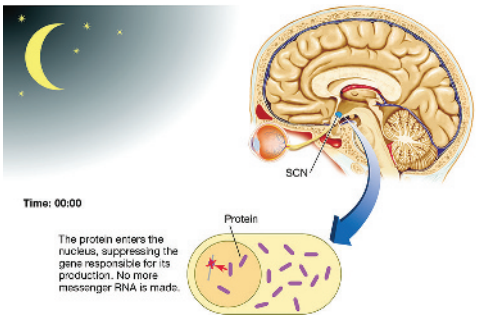
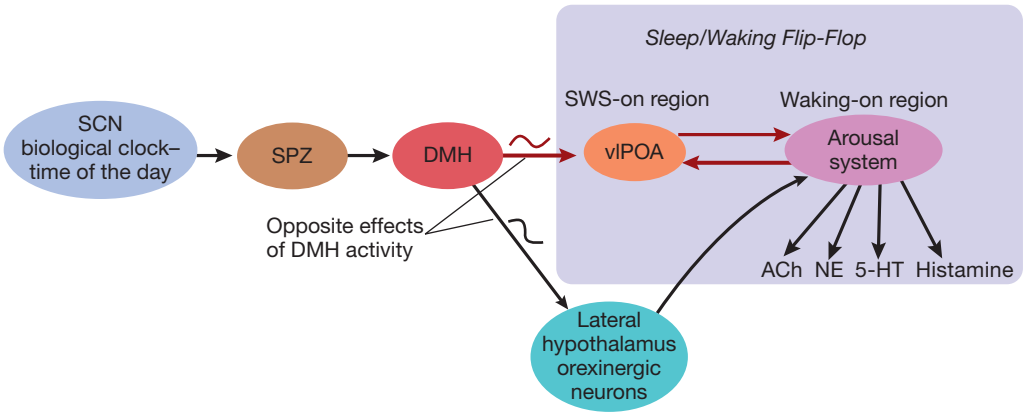

SCN
Time: 00:00
Protein
The protein enters the nucleus, suppressing the gene responsible for its production. No more messenger RNA is made.

Figure 9.19 Control of Circadian Rhythms in Sleep and Waking by the SCN

During the day cycle, the DMH inhibits the vlPOA and excites the brain stem and forebrain arousal systems, thus stimulating wakefulness.



This mechanism was first discovered in *Drosophila melanogaster*, the common fruit fly. Subsequent research with mammals revealed a similar system (Golombek and Rosenstein, 2010). The system involves at least seven genes and their proteins and two interlocking feedback loops. When one of the proteins produced by the first loop reaches a sufficient level, it starts the second loop, which eventually inhibits the production of proteins in the first loop, and the cycle begins again. Thus, the intracellular ticking is regulated by the time it takes to produce and degrade a set of proteins.

It appears that the circadian clock in the human brain works the same way. Toh et al. (2001) found that a mutation on chromosome 2 of a gene for one of the proteins involved in the feedback loops we mentioned earlier in this subsection (*per2*) is responsible for the **advanced sleep phase syndrome**. This syndrome causes a four-hour advance in rhythms of sleep and temperature cycles. People with this syndrome fall asleep around 7:30 p.m. and awaken around 4:30 a.m. The mutation appears to change the relationship between the zeitgeber of morning light and the phase of the circadian clock that operates in the cells of the SCN. Ebisawa et al. (2001) found evidence that the opposite disorder, the **delayed sleep phase syndrome**, may be caused by mutations of another gene, the *per3* gene, found on chromosome 1. This syndrome consists of a four-hour delay in sleep/waking rhythms. People with this disorder are typically unable to fall asleep before 2:00 a.m. and have great difficulty waking before midmorning. Allebrandt et al. (2010) found yet another set of gene variants (in the *clock* gene) that affect people's sleep duration.

advanced sleep phase syndrome A four-hour advance in rhythms of sleep and temperature cycles, apparently caused by a mutation of a gene (***per2***) involved in the rhythmicity of neurons of the SCN.

delayed sleep phase syndrome A four-hour delay in rhythms of sleep and temperature cycles, possibly caused by a mutation of a gene (***per3***) involved in the rhythmicity of neurons of the SCN.

pineal gland (*py nee ul*) A gland attached to the dorsal tectum; produces melatonin and plays a role in circadian and seasonal rhythms.

melatonin (*mell a tone in*) A hormone secreted during the night by the pineal body; plays a role in circadian and seasonal rhythms.

Control of Seasonal Rhythms: The Pineal Gland and Melatonin

LO 9.15 Describe how melatonin regulates seasonal rhythms.

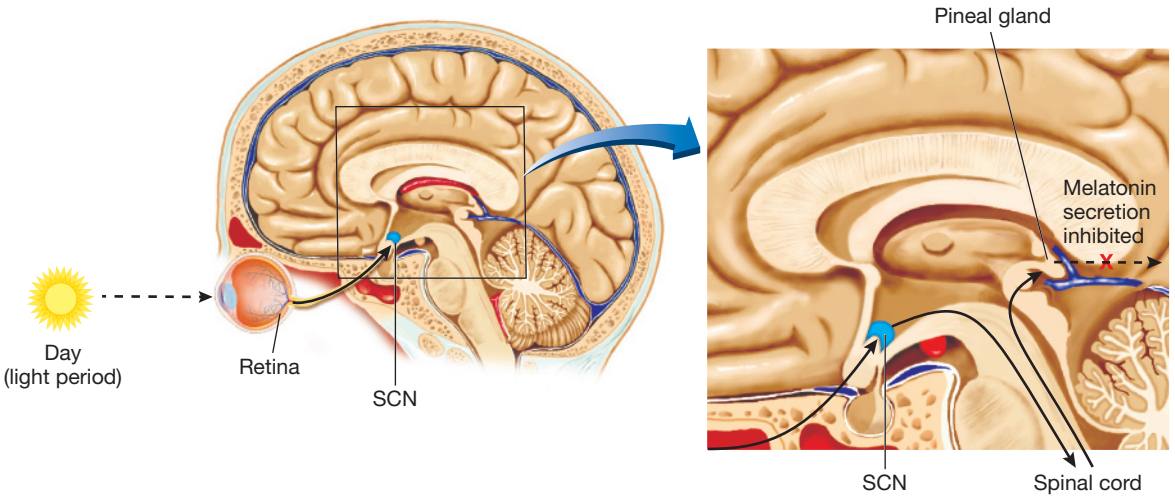
Although the SCN has an intrinsic rhythm of approximately twenty-four hours, it also plays a role in much longer rhythms. We could say that it is involved in a biological calendar as well as a biological clock.

The **pineal gland** sits on top of the midbrain, just in front of the cerebellum. (See Figure 9.20.) The pineal gland secretes a hormone called **melatonin**, so named because it has the ability in certain animals (primarily fish, reptiles, and amphibians) to turn the skin temporarily dark. In mammals, melatonin controls seasonal rhythms. Neurons in the SCN make indirect connections with neurons in the *paraventricular nucleus of the hypothalamus* (the PVN). The axons of these neurons travel all the way to the spinal cord, where they form synapses with preganglionic neurons of the sympathetic nervous system. The postganglionic neurons innervate the pineal gland and control the secretion of melatonin.

In response to input from the SCN, the pineal gland secretes melatonin during the night. This melatonin acts back on various structures in the brain (including the SCN, whose cells contain melatonin receptors) and controls hormones, physiological processes, and behaviors

Figure 9.20 The SCN and Pineal Gland

Melatonin is released by the pineal gland during the dark period. Light information, relayed from the retina to the SCN and PVN, suppresses the release of melatonin by the pineal gland. Disrupting this pathway interferes with seasonal rhythms that are controlled by day length.



that show seasonal variations. During long nights, a large amount of melatonin is secreted, and the animals go into the winter phase of their annual cycle. Lesions of the SCN, the PVN, or the pineal gland disrupt seasonal rhythms that are controlled by day length—and so do knife cuts that interrupt the neural connection between the SCN and the PVN, which indicates that this is one function of the SCN that is mediated through its neural connections with another structure. Furthermore, although transplants of fetal suprachiasmatic nuclei will restore circadian rhythms in animals with SCN lesions, they will not restore seasonal rhythms (Ralph and Lehman, 1991). (See Figure 9.20.)

Changes in Circadian Rhythms: Shift Work and Jet Lag

LO 9.16 Explain why shift work and jet lag result in changes of circadian rhythms.

When people abruptly change their daily rhythms of activity, their internal circadian rhythms, controlled by the SCN, become desynchronized with those in the external environment. For example, if a person who normally works on a day shift begins working on a night shift or if someone travels east or west across several time zones, his or her SCN will signal the rest of the brain that it is time to sleep at a time that does not correspond with the new environment or schedule. This disparity between internal rhythms and the external environment results in sleep disturbances and mood changes and interferes with people's ability to function during waking hours. Problems such as ulcers, depression, and accidents related to sleepiness are more common in people whose work schedules shift frequently (Drake et al., 2004).

Jet lag is a temporary phenomenon; after several days, people who have crossed several time zones find it easier to fall asleep at the appropriate time, and their daytime alertness improves. Shift work can present a more enduring problem when people are required to change shifts often. The solution to jet lag and to the problems caused by shift work is to get the internal clock synchronized with the external environment as quickly as possible. One way to start is to try to provide strong zeitgebers at the appropriate time. If a person is exposed to bright light before the low point in the daily rhythm of body temperature (which occurs an hour or two before the person usually awakens), the person's circadian rhythm is delayed. If the exposure to bright light occurs after the low point, the circadian rhythm is advanced (Dijk et al., 1995). In fact, several studies have shown that exposure to bright lights at the appropriate time helps to ease the transition to a new circadian pattern (Boulos et al., 1995). Similarly, people adapt to shift work more rapidly if artificial light is kept at a brighter level in the workplace and if their bedroom is kept as dark as possible (Horowitz et al., 2001).

The role of melatonin in seasonal rhythms is well established. Studies in recent years suggest that melatonin may also be involved in circadian rhythms. As we saw, melatonin is secreted during the night, which, for diurnal mammals such as ourselves, is the period during which we sleep. But although our species lacks strong seasonal rhythms, the daily rhythm of melatonin secretion persists. Thus, melatonin must have some functions besides regulation of seasonal rhythms. Studies have found that melatonin, acting on receptors in the SCN, can affect the sensitivity of SCN neurons to zeitgebers and can itself alter circadian rhythms (Gillette and McArthur, 1995; Starkey et al., 1995).

Module Review Biological Clocks

Thought Question

It was only with the development of cheap, effective lighting that many members of our species adopted the habit of staying up late and waking several hours after sunrise. Considering that our biological clock and the neural mechanisms it controls evolved long ago, do you think the changes in our daily rhythms impair any of our physical and intellectual abilities? If so, how? If not, why not?

Multiple-Choice Questions

LO 9.1 **1.** A person whose brain waves contain high-amplitude delta waves is most likely _____.
- **A.** in stage 3 of slow-wave sleep
- **B.** in stage 1 of slow-wave sleep
- **C.** dreaming
- **D.** in stage 2 of slow-wave sleep

LO 9.2 **2.** During REM sleep, there is increased cerebral blood flow to the _____ and decreased cerebral blood flow to the _____.
- **A.** extrastriate cortex; striate and prefrontal cortices
- **B.** striate and prefrontal cortices; extrastriate cortex
- **C.** striate and extrastriate cortices; prefrontal cortex
- **D.** prefrontal cortex; striate and extrastriate cortices

LO 9.3 **3.** The rebound phenomenon noted after deprivation of REM sleep suggests that _____.
- **A.** there is a physiological need for stage 1 slow-wave sleep
- **B.** the function of REM sleep is to rest the brain
- **C.** emotional wellbeing requires slow-wave sleep
- **D.** there is a physiological need for a certain amount of REM sleep

LO 9.4 **4.** _____ sleep is to facilitation of nondeclarative memory consolidation as _____ sleep is to facilitation of declarative memory consolidation.
- **A.** slow-wave; Stage 1
- **B.** REM; Stage 1
- **C.** REM; slow-wave
- **D.** slow-wave; REM

LO 9.5 **5.** Administration of a(n) _____ would be expected to promote sleep.
- **A.** adenosine antagonist
- **B.** adenosine agonist
- **C.** hypocretin agonist
- **D.** serotonin antagonist

LO 9.6 **6.** _____ is to increased norepinephrine as _____ is to decreased norepinephrine.
- **A.** Wakefulness; slow-wave sleep
- **B.** Stage 1; slow-wave sleep
- **C.** REM sleep; slow-wave sleep
- **D.** Slow-wave sleep; REM sleep

LO 9.7 **7.** Which statement is true?
- **A.** Orexin is necessary to stabilize the sleep-wake cycle.
- **B.** Serotonin is necessary to stabilize the sleep-wake cycle.
- **C.** Histamine is necessary to stabilize the sleep-wake cycle.
- **D.** Acetylcholine is necessary to stabilize the sleep-wake cycle.

LO 9.8 **8.** Secretion of orexin in the _____ produces _____.
- **A.** REM-OFF area; wakefulness
- **B.** REM-ON area; a loss of slow-wave sleep
- **C.** preoptic area; wakefulness
- **D.** REM-OFF area; cataplexy

LO 9.9 **9.** _____ is a sleep disorder that involves a buildup of carbon dioxide in the blood during sleep.
A. Situational insomnia
B. Sleep apnea
C. REM disorder
D. Narcolepsy

LO 9.10 **10.** Which statement is true?
A. Orexin-A mutations result in narcolepsy.
B. Orexin-B mutations result in narcolepsy.
C. Serotonin mutations result in narcolepsy.
D. Histamine mutations result in narcolepsy.

LO 9.11 **11.** The primary symptom of REM-sleep behavior disorder is(are) _____.
A. attacks of cataplexy
B. a depressed mood on awakening
C. motor movements during slow-wave sleep
D. the ability of a person to move during REM sleep

LO 9.12 **12.** Somnambulism is synonymous with _____.
A. sleep attack
B. dreaming while awake
C. sleepwalking
D. cataplexy

LO 9.13 **13.** _____ is an example of a _____.
A. Light; zeitgeber
B. Colder night temperature; pacemaker
C. Melatonin; pacing stimulus
D. Warmer day temperature; zeitgeber

LO 9.14 **14.** Which statement is true of melanopsin?
A. Melanopsin in rods is a cue that resets SCN clock cells.
B. Melanopsin is found within cones but not rods.
C. Melanopsin activity is suppressed by light.
D. Melanopsin is found within ganglion cells.

LO 9.15 **15.** At night, one would expect melatonin levels to be _____.
A. the same as during the day
B. reduced from daily levels
C. increased from daily levels
D. fluctuating from low to moderate levels

LO 9.16 **16.** A potential treatment for jet lag is to administer _____ at _____.
A. amphetamine; noon
B. melatonin; bedtime
C. alcohol; boarding time
D. amphetamine; bedtime

Discussion Questions

LO 9.2 **1.** Compare the characteristics of non-REM sleep with that of REM sleep.

LO 9.6 **2.** Compare the relative levels of neurotransmitters when awake, in REM sleep, and in slow-wave sleep.

LO 9.7 **3.** Compare the on-off flip-flop sleep-wake system to the idea that, as you have seen with other neuroscience topics, an event either happens or it does not.

LO 9.10 **4.** Explain the relationship between REM sleep, narcolepsy, and antidepressant medications.

LO 9.14 **5.** Evaluate the hypothesis that the suprachiasmatic nucleus (SCN) acts as the primary biological clock.